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ORIGINAL ARTICLES

CONGENITAL MEGACOLON

By ORVAR SWENSON, M.D.
Boston

TWO years ago I had the privilege of presenting to this Academy our concepts of the pathology, the related dysfunction of the colon, and the surgical treatment of congenital megacolon.[1] I should now like to relate our interim clinical experience with these patients and particularly to stress diagnostic criteria of this disease.

Children with constipation should, from a practical standpoint, be divided into two groups: those with chronic constipation on a habit or psychologic basis who should be treated medically; and those with congenital megacolon who should be treated surgically. The differentiation of the two groups is usually not difficult from the information gained in taking the history and performing the physical examination. The large majority of our patients with congenital megacolon have a history of constipation from birth. Often obstipation, vomiting and abdominal distention have been of such prominence during the first few days of life that a diagnosis of intestinal obstruction has been entertained and exploration occasionally performed. A considerable number of infants die of congenital megacolon in the first weeks of life. The surviving infants continue to have varying amounts of constipation with intermittent abdominal distention and require frequent enemas or some other aid in evacuation. In contrast to this the children with chronic constipation on a habit basis have histories of no symptoms until they are 2 or 3 years of age, and abdominal distention is rarely present. Furthermore, there is usually a history of parental overanxiety concerning intestinal function, and this emotional attitude toward the child's problem accounts for their tendency to exaggerate symptoms.

Further differentiation of the two groups can be made on physical examination, for the child with congenital megacolon will have abdominal distention and increased anteroposterior diameter of the chest with superior and lateral flaring of the rib margins. Frequently there is a large fecal impaction in the lower abdomen, which cannot be palpated

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E. Mead Johnson Award Address, read at the Annual Meeting, American Academy of Pediatrics, Chicago, Oct. 22, 1952.

From The Boston Floating Hospital (for Infants and Children) and the Department of Surgery, Tufts College Medical School, Boston.

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FIG. 1. Typical lesion of congenital megacolon. Note nondistended rectum and rectosigmoid with dilatation of sigmoid.

on rectal examination, indicating that the impaction is above the congenital lesion. Children with chronic constipation usually have no abdominal distention or deformity of the chest cage, and when a fecal impaction is present it can always be palpated on rectal examination indicating the absence of a congenital lesion in the lower colon.

An absolute diagnosis of congenital megacolon can only be made by roentgen examination, and there is considerable misconception of the criteria necessary to establish the diagnosis. The original radiographic examinations were performed by Dr. E. B. D. Neuhauser. Enlargement of the colon *per se* is of secondary importance diagnostically; for while it invariably occurs in congenital megacolon it frequently is due to other causes, particularly chronic constipation. To establish the diagnosis of congenital megacolon there must be definite evidence of a segment of nondistended colon extending from the anus to the rectosigmoid. Proximal to this the sigmoid is dilated, and there is an accumulation of gas and fecal material (Fig. 1).[2] Narrow areas 2 to 3 cm. in length in the sigmoid and rectosigmoid with some dilatation of the colon above and below are usually artifacts and insufficient to make a diagnosis of congenital megacolon.

The technic of the roentgen examination was devised by Dr. E. B. D. Neuhauser. A straight catheter is inserted through the anal canal, and a small amount of barium is injected as the patient is observed on the fluoroscopic screen in an oblique or lateral position. The contrast media is allowed to flow in slowly, and as the sigmoid begins to fill the flow of barium is stopped. Should the sigmoid be completely filled it may overlap and obscure the lesion which must be identified to establish the diagnosis of congenital megacolon.

When the diagnosis has been confirmed radiographically the patient should have resection of the aganglionic portion of the colon. The operation of resection of the rectum and rectosigmoid with a pull-through anastomosis is technically a difficult one. There are many problems connected with it, and there can be serious complications unless the surgeon

FIG. 2. A. Preoperative RG of patient with congenital megacolon. This postevacuation film demonstrates inability of colon to empty properly. B. RG 14 mo. after operation. Note ability of colon to empty normally.

is experienced and familiar with this operative procedure. Recently State has advocated that a segmental resection be performed for this disease leaving the aganglionic rectum in place.[3] He advocated an incomplete resection of the involved bowel because he feared resection of the rectum and rectosigmoid might cause impotence in the male patients. Three of our patients have been adult males, and following resections including the rectum and rectosigmoid ejaculation is normal. Thus, State's hypothetic objection to complete excision of the lesion has not been borne out in our experience.

Furthermore, if the resection is limited to the lesion extending above the pelvic peritoneum about half the patients would not be helped at all, because in our experience 47% of the patients have lesions which only involve the colon below the pelvic peritoneum. Most important of all, a partial resection of the lesion is not reasonable from a theoretic standpoint because we see patients with congenital megacolon with lesions no longer than would be left in place with an anterior resection. In the past such incomplete resection, while helping some patients, has not completely relieved them; and there has been a recurrence of the disease in some.[4] It seems reasonable that if surgery is to be used in the treatment of this disease a complete removal of the pathology should be performed.

The postoperative results of resection of the entire aganglionic segment have been extremely gratifying. There has been one recurrence in 108* patients, and in that instance there was incomplete resection of the aganglionic bowel. The lesion extended to the splenic flexure, and only the distal half of it was resected. In order to guard against such recurrence frozen sections are made at operation to determine that ganglion cells are present at the proximal line of resection. There have been four postoperative deaths in 108 patients, and in each instance the patient was under 6 months of age. The surviving patients have

* The author operated on 65 patients at Children's Hospital, Boston.

one to two bowel movements a day and require no special diet, laxatives or enemas. The abdominal distention gradually disappears, and the abdominal contour is normal one year after operation. Barium enema examinations have demonstrated the dilated bowel returns to essentially normal size. Most important is the ability of the colon to completely empty (Fig. 2).

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PARAHEMOPHILIA (OWREN'S DISEASE)

By BERNARD REDNER, M.D., HOWARD SCALETTAR, M.D., AND MURRAY WEINER, M.D.
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THE clotting of blood is due to the conversion of the soluble protein, fibrinogen, into an insoluble form, fibrin. This conversion, it is believed, occurs as a result of an enzyme, thrombin, which normally exists in the plasma in an inactive precursor form, prothrombin. Prothrombin requires for its activation both calcium and a factor present in platelets or tissue extracts usually called thromboplastin.

In the past 20 years the estimation of prothrombin has become clinically important. The clotting time of oxalated plasma after the addition of a standard excess of thromboplastic tissue extract and an optimal amount of calcium is generally considered to be a function of the prothrombin concentration (one-stage method). In addition, prothrombin can also be estimated by defibrinogenation of the plasma specimen, converting all the prothrombin to thrombin, and then testing the rate at which various dilutions of the specimen will clot aliquots of a standard fibrinogen solution under standard conditions (two-stage method).

Recent advances in our knowledge of the clotting mechanism have demonstrated that the enzyme activity attributed to prothrombin is not the result of a single protein moiety. In 1944, Owren[1,2] described a case of severe hemorrhagic diathesis in a 29 year old female, which condition dated back to age 3 and was apparently due to a marked hypoprothrombinemia. This apparent prothrombin deficiency, however, was largely corrected by the addition of prothrombin-free plasma. This indicated that the deficiency was not due to a lack of prothrombin itself, but rather to some other factor essential to prothrombin activity. Additional study led Owren to the identification of a new component of normal blood essential to the normal clotting process.[3] Since the classical theory of coagulation calls for four essential factors (fibrinogen, calcium, thromboplastin and prothrombin), Owren called this new component "Factor V." His factor is probably identical with the labile factor described independently by Quick,[4,5] and also the Ac (accelerator) globulin of Seegers.[6,7]

Since 1944, the congenital deficiency of Factor V, called parahemophilia or Owren's disease, has been described in 5 reports of 11 additional cases (table 1). Two additional cases, described by Rhoads in 1941[13] and by Crockett[14] in 1949, were reported as idiopathic hypoprothrombinemia. Although no definite diagnosis was established, they probably fall into the category of congenital parahemophilia.

Acquired Factor V deficiency has been reported to occur in sepsis,[15,16] liver disease,[17] metastatic carcinoma of the prostate[18] and amyloidosis.[19] The condition is to be distinguished from hypofibrinogenemia, increased fibrinolysin activity, and excessive circulating inhibitor substances, all of which may cause an apparent decrease in prothrombin activity in spite of normal prothrombin content.[20,21]

From the Pediatric Service, Beth El Hospital, Brooklyn, and the Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, Welfare Island, New York City.

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TABLE 1

SUMMARY OF REPORTED CASES OF PARAHEMOPHILIA

Author	Age of Patient at Time of Report	Year	Country	Sex	Age at Onset of Bleeding	Severity
Owren[1,2]	29	1944	Norway	F	3	Severe
Frank[8]	29	1950	Germany	M	3	Moderate
Stohlman[9]	20	1951	U. S.	F	8	Moderate
DeVries[10] (Siblings)	15	1951	Israel	M	Childhood	Mild
	6	1951	Israel	M	Childhood	Mild
	11	1951	Israel	F	Childhood	Mild
Brink[11]	27	1952	S. Africa	F	5	Severe
	32	1952	S. Africa	F	Childhood	Severe
	13	1952	S. Africa	M	5	Moderate
Alexander[12] (Siblings)	17	1952	U. S.	F	5	Severe
	15	1952	U. S.	F	No clinical bleeding	
	4	1952	U. S.	M	No clinical bleeding	

This paper presents a report of a 5 year old female who suffers from severe hemorrhages related to that rare congenital clotting abnormality which is manifested by a markedly prolonged prothrombin time in spite of a normal plasma content of prothrombin itself. The unusual physiologic disturbances present in this case supplied valuable clues to the nature of normal physiologic mechanisms. The laboratory data will be discussed in the light of the newer theories of coagulation.

CASE REPORT

M. B., a 5 yr. old girl of Puerto Rican parentage, was admitted to the Beth-El Hospital because of severe nasal hemorrhage uncontrolled by ordinary measures.

Her delivery and early infancy were unremarkable. She was the first child of normal parents. Family history was negative except that the mother had a minimal inactive tuberculous pulmonary lesion. A younger sibling, a brother aged 2½ yr., has occasional nasal bleeding.

At 10 mo. of age the child had her first episode of severe bleeding which consisted of an oral hemorrhage. The bleeding persisted for several days and then subsided spontaneously. There was no history of contagious disease or severe infection. During the next 2 yr. there were repeated episodes of epistaxis, melena and ecchymosis, all of which subsided spontaneously. At 3 yr. of age a tonsillectomy and adenoidectomy was done at another hospital. Bleeding was profuse and the child remained hospitalized for 15 days during which time she required several blood transfusions. At 4 yr. of age, she was hospitalized again because of uncontrollable bleeding from a large hematoma of the scalp which had been incised by the family physician. Again, at age 4½ yr., a hematoma of the finger was incised and transfusion was necessary to control bleeding. A fourth hospital admission because of severe epistaxis once again required blood transfusion.

At age 5, the child was admitted to Beth-El Hospital for the first time because of severe epistaxis and numerous ecchymotic areas over her body. On physical examination, the patient was a well developed female child who did not appear to be acutely ill. There were both fading and fresh ecchymotic areas scattered over her body and fresh blood exuding from the left nostril. There were no conjunctival hemorrhages. Fundi were not remarkable. No nodes were palpable. Heart and lungs were normal. Liver and spleen were not felt at any time.

During her hospitalization, repeated urinalyses showed several episodes of microscopic hematuria, and on one occasion, gross hematuria. Stools were occasionally tarry, repeatedly guiaic-positive and at no time showed ova or parasites. A battery of liver function tests (A—icteric index, cephalin flocculation, thymol turbidity, serum bilirubin, bromsulfphthalein retention and glucose tolerance) and other blood chemical studies (B—blood urea nitrogen, serum albumin and globulin, cholesterol,

TABLE 2

PROTHROMBIN TIME DETERMINATIONS

	One-stage prothrombin times of whole plasmas* (sec.)		
	Unaltered	Equally diluted with	
		Normal plasma	Prothrombin-free plasma
Patient	31 to 52	19	20
Mother	20	18	20
Father	15	—	—
Brother	15	—	—
Normal plasma	14 to 17	14 to 17	15 to 19
Prothrombin-free plasma†	no clot	15 to 19	no clot

* Thromboplastin preparation simplastin® used in these prothrombin time determinations, and fibrinogen and prothrombin-free plasma employed in these studies were prepared from material supplied by Dr. George Phillips, Chilcott Laboratories, Morris Plains, N. J. Each test consists of timing clot formation after addition of 0.1 cc. plasma or mixture of plasmas to 0.2 cc. reconstituted calcium-thromboplastin preparation (simplastin®).

† Prothrombin-free plasma may be prepared by stirring normal plasma with freshly prepared suspension of barium sulfate, and filtering.[11]

calcium, phosphorus and alkaline phosphatase) were consistently normal. Chest RG, skull, long bones and barium enema revealed no pathology.

Blood cellular components were normal except for a moderately severe anemia secondary to blood loss. There was a mild leukocytosis, moderate reticulocytosis and normal active bone marrow. Red cell fragility to hypotonic saline was normal. Investigation of the hemostatic and coagulation mechanisms revealed the following:

1. Capillary fragility test—Negative (no petechiae after 5 min. of 30 mm. negative pressure).
2. Bleeding time—3 min.
3. Lee-White clotting time (3 tubes)—21 to 29 min.
4. Fibrinogen concentration—362 mg./100 cc.
5. Platelet count—340,000/cmm.—direct method.
6. Clot retraction—normal (complete in less than ½ hr.).
7. Fibrinolysin activity—no solution of patient's clot or normal clot by patient's serum in 48 hr.
8. Plasma prothrombin times—summarized in table 2—one-stage method.[23]
9. Serum prothrombin time (prothrombin consumption) using purified fibrinogen[22]—activity only slightly less than that of corresponding plasma, indicating very little prothrombin consumption.

Throughout most of her hospital stay, the child bled from her nose, urinary and gastrointestinal tract, and continued to develop new ecchymoses. Prolonged therapy with vitamin K parenterally had no effect on the hemorrhages or prothrombin time. Repeated blood transfusions eventually controlled the bleeding and she was discharged improved with a prothrombin time of 31 sec.

Patient's blood was also studied by Dr. Mario Stefanini and Dr. Walter Seegers. Dr. Seegers found a marked deficiency of Ac globulin by the 2-stage method, with near-normal prothrombin activity. Dr. Stefanini also found a marked Ac globulin deficiency by Seegers' method, and similar labile factor deficiency by the Quick method, with near-normal stable component (prothrombin) activity. He also demonstrated the capacity of the patient's plasma to correct both dicumarol®-induced and other true prothrombin deficiency, but not that of known labile factor deficiency. The patient's plasma presented a normal electrophoretic pattern.

DISCUSSION

In parahemophilia the basic defect consists of a congenital deficiency in a portion of the prothrombin complex. The deficient factor (Factor V, Ac globulin, Labile factor) is an

essential component for the transformation of prothrombin to thrombin. Without it, the coagulation mechanism may be sufficiently disturbed to result in clinical hemorrhage, as demonstrated in this case.

The deficiency of Factor V is most simply detected by a prolongation of the one-stage prothrombin time. This is correctable by the addition of fresh prothrombin-free plasma which contains Ac globulin. It is not correctable by the addition of stored or heated plasma, which contains prothrombin, but has lost its labile factor activity.

Factor V is a heat labile protein, and is destroyed on prolonged standing. Its synthesis is unrelated to vitamin K. Unlike prothrombin itself, little or none is adsorbed in organic gels. It is not adsorbed or precipitated by barium sulfate, but is adsorbed on magnesium hydroxide. It is less soluble in ammonium sulfate than prothrombin and is more sensitive to acid, alkali and heat. In stored plasma citrated in the customary fashion, it is largely destroyed in about one week.[7, 24] The place of Factor V in the clotting mechanism is shown in a simplified scheme (Fig. 1).

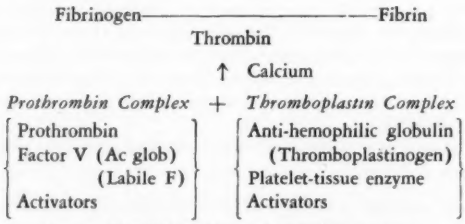

FIG. 1. Simplified scheme of clotting process.

Agreement is not universal as to whether Factor V unites chemically with prothrombin to form a more complex, active molecule, or whether it serves only as an accelerator of prothrombin conversion. The activity of Factor V itself may be altered from its initial plasma state during prothrombin conversion.[3] The high serum prothrombin activity (poor prothrombin consumption) in the authors' case is evidence of poor prothrombin conversion in the absence of sufficient Factor V. Whatever the mechanism, it is clear from observations such as these here reported, that the enzyme activity ordinarily attributed to prothrombin cannot be demonstrated in the absence of Factor V.

The over-all prothrombin activity as estimated by the one-stage prothrombin time technics is perhaps best labeled a function of the prothrombin complex (Fig. 1). However, one-stage prothrombin times may be altered by factors other than changes in the components of the prothrombin complex. Many inhibitor substances, both extrinsically added or naturally occurring, may prolong prothrombin time. These can be detected by demonstrating an inhibiting effect on normal plasma, or by the disappearance of inhibitor activity on dilution.[25, 26] A lack of fibrinogen may also influence the one-stage prothrombin time. This defect is easily recognized by its complete correction on the addition of pure fibrinogen. The presence of excessive fibrinolytic activity may interfere with clot formation in the one-stage test.[21] Observation for excess fibrinolysis should be made before any unusual apparent prothrombin defect by the one-stage method is attributed to the prothrombin complex. When all the above possibilities have been ruled out, a prolonged one-stage prothrombin time may be considered to be due to a deficiency in the prothrombin complex, and may be further defined by its reponse to prothrombin-free plasma or purified prothrombin. A prolonged prothrombin time due to Factor V deficiency is corrected by the

addition of fresh prothrombin-free plasma, but not by the addition of aged or heated plasma. In all clotting tests which involve the addition of various plasma fractions or reagents, the very considerable influences of nonspecific protein and salt concentration on clotting time must be taken into account.

The total number of active moieties involved in both the prothrombin complex and the thromboplastin complex is yet to be determined. There is evidence that prothrombin itself exists at least in part in a less active form,[27] and that still more accessory activity becomes manifest during the formation of thrombin, such as that labeled Factor VI by Owren,[3] or serum Ac globulin by Seegers.[7] Similarly, the thromboplastin complex now appears more involved than simply a two component plan of platelet-tissue enzyme plus antihemophilic globulin. Some of these finer definitions of the normal clotting mechanism may be uncovered by careful study of unusual clinical abnormalities in coagulation.

Summary

A case of parahemophilia in a five year old child has been presented. This case follows the pattern first described by Owren, namely, a congenital hemorrhagic disease with deficient prothrombin activity by the one-stage method correctable by the addition of prothrombin-free plasma. The positive laboratory findings consisted of a prolonged prothrombin time and a slightly prolonged clotting time. Ac globulin deficiency was confirmed both by Dr. Seegers and by Dr. Stefanini. There was no abnormal fibrinolytic activity or fibrinogen deficiency. Serum prothrombin activity indicated that a deficiency of Factor V was accompanied by decreased prothrombin consumption. There was no response to prolonged vitamin K therapy. Blood and plasma transfusions temporarily controlled bleeding, although at no time was a normal one-stage plasma prothrombin time obtained.

Acknowledgment

The authors wish to express their gratitude and appreciation to Dr. Walter H. Seegers, Professor of Physiology and Chairman, Wayne University School of Medicine, and to Dr. Mario Stefanini of the New England Center Hospital for their cooperation in studying the blood of the patient here reported.

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SPANISH ABSTRACT

Un Caso de Parahemofilia (Enfermedad de Owren)

Los autores presentan el caso de una niña de cinco años de edad que ingresó al hospital debido a una hemorragia nasal incontrolable; desde los diez meses de edad se venían presentando hemorragias en diversos sitios del organismo. El cuadro encaja en el descrito por Owren de hemorragia congénita por actividad defectuosa de la protrombina, corregible con plasma libre de protrombina. Las pruebas de laboratorio mostraron tiempo de protrombina prolongado y tiempo de coagulación ligeramente prolongado; deficiencia del factor V de la coagulación, acompañada por consumo disminuído de protrombina (el factor V es la denominación dada por Owren al factor que probablemente corresponda al factor lábil descrito por Quick y al factor de aceleración de la coagulación [globulina Ac] de Seeghers); no se encontró deficiencia de fibrinógeno ni de la actividad fibrinolítica. No se observó respuesta a la terapéutica prolongada con vitamina K; las transfusiones sanguíneas y de plasma controlaron temporalmente la hemorragia.

Los autores hacen consideraciones fisiológicas sobre el factor V.

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INTERSTITIAL "PLASMA CELL" PNEUMONIA OF PREMATURE AND YOUNG INFANTS

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THE purpose of this report is to call the attention of American physicians to the occurrence in Europe of an interesting type of infantile pneumonia, which appears to be relatively unknown in the United States. It is characterized by a marked predilection for premature or immature infants 1½ to 4 months of age, an almost asymptomatic course until late in the illness and by a widespread infiltration of both lungs with mononuclear cells resembling plasma cells. It is of undetermined etiology, frequently fatal and fairly common in many parts of Europe. Between 1941 and 1949, 707 cases were reported in Switzerland,[1] a country with a total population of about five million. Of this number, 154 (22%) were fatal cases.

The authors have been unable to find a report in the American literature dealing with the occurrence of this disease in the United States. They believe it is a clinical entity and think it unlikely that it could be overlooked or confused pathologically with other types of pneumonia. The single exception to the latter statement is luetic pneumonia. This condition shows considerable pathologic similarity with interstitial plasma cell pneumonia. The differentiation is greatly facilitated by the other typical features of both diseases.

It is remarkable that a disease so frequently seen and well known in Switzerland and several other European countries should remain unnoted in the United States. So that the reader may decide the latter point for himself, as well as be alerted to the possible future occurrence of the illness, this report has been written.

Just how long this type of pneumonia has been present in Europe is a disputed point, but the preponderant opinion is that it dates chiefly from about 1938, when Ammich[2] and Benecke[3] reported on it.

This report is based on the autopsy findings at the Institute of Pathology at the University of Zürich in 35 fatal cases of this type of pneumonia, on the clinical observation of a number of cases, and a review of the literature.

CLINICAL DESCRIPTION

The onset of interstitial plasma cell pneumonia is insidious and so gradual as to make the actual date of onset difficult to determine. An infant, usually a premature about 6 weeks to 4 months of age, without immediately associated evidence of an upper respiratory tract infection, in the majority of cases, begins to look poorly, becomes restless or languid in behavior and does not take its feedings in the usual manner.* Gradually the infant's respirations increase in frequency; bluish shadows may appear under its eyes and around its mouth. On examination at this stage local signs over the lung fields may be entirely

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* An experienced nurse may note this change in behavior or it may be entirely overlooked.

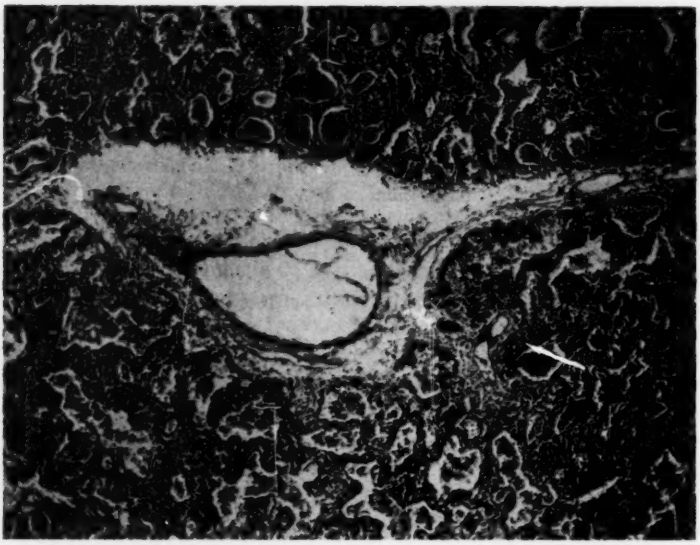


FIG. 1. J. G., aged 3 mo., birth wt. 2730 gm. Air space surrounding empty blood vessel probably not artefact but is due to interstitial emphysema. Surrounding lung tissue shows compressed alveoli and thickened interalveolar septa. Thickening is due to infiltration with mononuclear cells most of which resemble plasma cells. Exudate filling alveoli has shrunken away from alveolar walls during fixation. (× 60. Hematoxylin and eosin.)

absent, with little or no cough, and no fever or weight loss. With progression of the pneumonic infiltration, respiration continues to increase in frequency and is almost entirely abdominal and characterized by prominent flank-motion. This rapid respiratory movement of the lateral abdominal wall is considered by Willi[4] to be the most important clinical finding. After 1 or 2 weeks, or longer, the fully developed clinical picture may unfold rather suddenly with pronounced dyspnea, dilation of nostrils, retraction of the sternum, cyanosis and extremely rapid respiration—marking the first recognition of the disease clinically. The infant's face shows a bluish-white pallor and a tortured, anxious expression. Its head is covered with perspiration. The slightest activity is followed by an increase in dyspnea, and only rest and the constant administration of oxygen are of help.

Physical examination may reveal areas of fine crepitant rales, particularly if the infant is made to cough or to breathe deeper than usual. Slight impairment of resonance and a bronchial quality to the breath sounds may also be detected in some areas, but marked dullness and bronchial breathing are rarely found, even in this fully developed stage of the disorder. Interstitial emphysema often develops at this time (Fig. 1) and may be accompanied by the formation of subpleural blebs (Fig. 2), mediastinal emphysema, subcutaneous emphysema or even a tension pneumothorax. In probably no other disease of infancy is interstitial emphysema as frequent, diffuse, markedly developed or varied in form (mediastinal, perithymic, perivascular, pericardiac, subcutaneous) as it is in the late stages of interstitial plasma cell pneumonia.

If the illness has progressed to the late stage just described, death often follows within a few days. However, survival is still possible, with recovery after a stormy period lasting

FIG. 2. R. H., aged 2 mo., birth wt. 2700 gm. Mediastinal emphysema. Air pressure has blown up filmy mediastinal tissues into foam-like network of glistening air sacs. On right, thymus lies over large sac. Below it arrow points to subpleural air bleb at lung margin.

5 to 10 days. Even in this late stage there is usually only an inconstant low grade fever or none at all, and not much cough, although in an occasional case a persistent cough and a higher irregular fever are present. The weight curve is usually affected only slightly and even in the stage of severe dyspnea there may be only a stabilization of weight rather than a weight loss.

The white blood cell count is variable, as is also the erythrocyte sedimentation rate. Neither are of real aid in the diagnosis. Cold-agglutinins are not present.

The duration of the illness is difficult to estimate since the time of onset is so poorly defined and the early stage so lacking in signs and symptoms. In most instances, it could probably be considered to be from 4 to 6 weeks. It would appear that an interstitial infiltration, which gradually encroaches on alveolar air space, is present for some time and may progress quite far without being reflected in striking clinical symptoms. A critical point evidently exists, after which further interference with alveolar function begins to cause great distress and threaten life.

In one of the authors' cases the illness of the patient was not apparent to the parents until two days before death. In this instance the initial stage was presumably overlooked as is, indeed, often the case. In another infant, although under constant observation in the hospital because of prematurity, illness was not apparent until three days before death. Walther[5] described two similar cases in which sudden unexpected death occurred and Gormsen[6] reported a patient who died suddenly after two days of food rejection. All five of these infants were prematurely born and at autopsy all showed a typical bilateral widespread interstitial pulmonary infiltration with mononuclear cells resembling plasma cells. While

such sudden and unexpected death is not the rule, these five cases serve to illustrate how easily the initial phase of the illness is overlooked and how rapid and severe the downhill course can become.

The justification for the assumption that such cases are of longer duration than the clinical course indicates lies chiefly in the consistency with which roentgenologic evidence of pulmonary infiltration may be found early in the course of the disease, when clinical symptoms are lacking. Faint diffuse opacities are scattered over both lung fields on a slightly ground-glass background. Freudenberg[7] suggested taking routine chest films on all patients exposed to interstitial plasma cell pneumonia when the disease was present on the hospital ward, in order to pick up the early cases. Tobler[8] relied on an increase in the respiratory rate to reveal the onset of the disease. This necessitated carefully repeated daily counting of respiration during sleep on each infant, and the establishment in this way of a base-line for each case. A rate of over 40 to 50/minute was considered suspicious in premature infants.

The two measures cited, routine chest films and routine respiratory rate count, are mentioned particularly since their use implies the considerable difficulty which is otherwise encountered in recognizing the presence of the disease in its early stages. By employing one or the other of the methods cited and following suspect cases roentgenographically, it came to be recognized that many infants had a mild form of the disease which otherwise would not have been apparent.

Pathology

Gross Pathology: The lungs are typically pale-gray and heavy, and appear large. They contain little air and, therefore, do not collapse when the thorax is opened. The lungs are

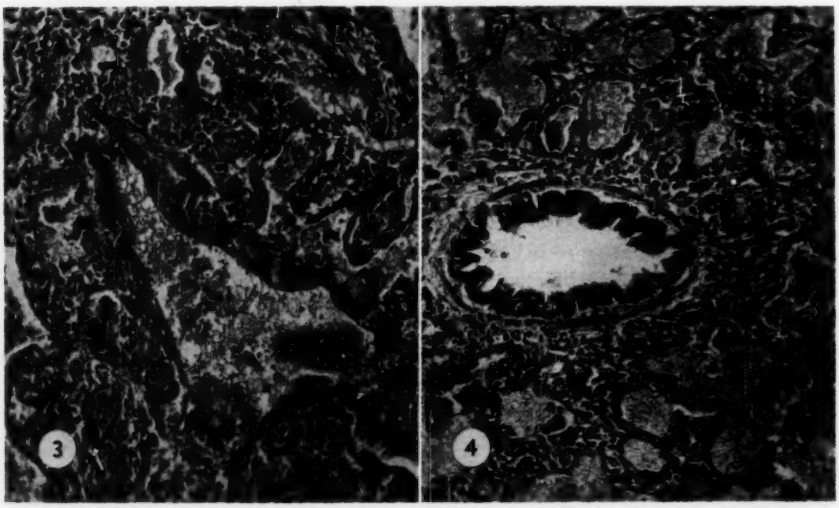


Fig. 3. H. B., aged 2½ mo., birth wt. 2370 gm. Triangle-shaped alveolar duct whose wall is partially lined with hyalin-like material. Latter somewhat resembles asphyxial membrane occasionally seen in premature infants who have lived short time. (× 163. Hematoxylin and eosin.)

Fig. 4. U. H., aged 3¼ mo., birth wt. 1700 gm. Compressed but intact bronchiolus shows epithelial cells which are pressed into folds. In some areas (upper right) amorphous exudate in alveoli is beginning to show hyaline-like changes. (× 180. Hematoxylin and eosin.)

firm in consistency practically throughout and on cut sections present a uniformly solid appearance. Only in a small portion of the lungs, usually that near the anterior edge of the upper and middle lobes, are air-filled alveoli apparent. These represent that small portion of the lungs which were able to function up to the time of death. In these thin anterior marginal areas multiple subpleural air blebs are also characteristically seen (Fig. 2). They are due to interstitial emphysema which has reached the surface of the pleura where vari-sized, sometimes extremely large, air pockets are formed.

The bronchi and pleura present a normal appearance. The hilar lymph nodes appear only slightly enlarged. Frequently mediastinal emphysema and, occasionally, a spontaneous pneumothorax are present. Other organs show no consistent changes, although the heart is often somewhat enlarged.

Microscopic Pathology: At first glance a microscopic section may show little resemblance to lung tissue, alveolar septa being so widened by cellular infiltration that many of them press against each other, thus presenting a fairly solid and markedly cellular appearance (Fig. 1). In some cases alveolar spaces are thus completely obliterated; in others they are reduced in size and partially or entirely filled with exudate. The alveolar ducts are likewise compressed or filled with exudate (Fig. 3). Only an occasional alveolus or alveolar duct is dilated, reflecting emphysema. In all, remarkably little air-containing tissue is seen. The luminae of smaller bronchioles may contain exudate, but otherwise—save for compression—the bronchioles and bronchi are unchanged (Fig. 4). Their epithelium

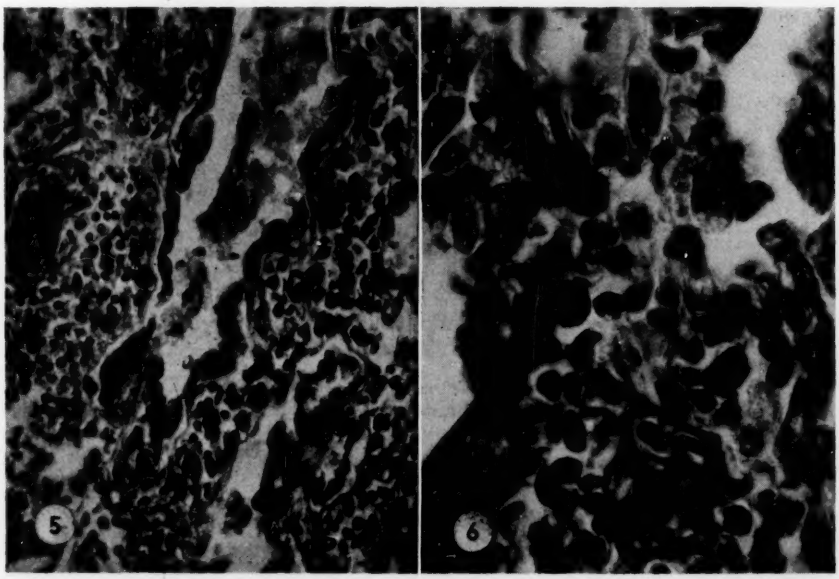
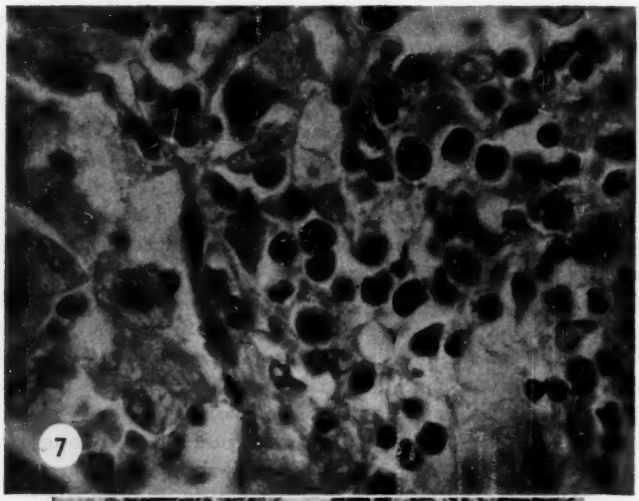


FIG. 5. R. U. aged 2½ mo., birth wt. 1500 gm. Infiltration with mononuclear cells, most of them resembling plasma cells, surrounds and compresses alveolus which has elongated shape and is partially filled with exudate. Its lining cells are swollen, those of adjacent alveolus (lower right) are detached. Dark oval mass to left is blood vessel filled with blood. (× 328. Romanovsky.)

FIG. 6. J. G., aged 3 mo., birth wt. 2730 gm. Mononuclear cells, many of which resemble plasma cells, infiltrating wall between 2 alveoli. Same case as is illustrated in Fig. 1. (× 490. Hematoxylin and eosin.)



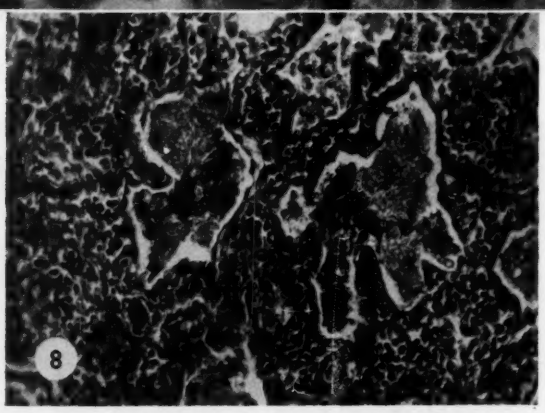


FIG. 7. F. S., aged 3 mo., birth wt. 1300 gm. Interstitial infiltration of cells resembling plasma cells and histiocytes. To left is alveolus containing large swollen cast-off lining cells. (× 540. Hematoxylin and eosin.)

FIG. 8. E. H., aged 2¾ mo., birth wt. 3440 gm. Alveoli filled with exudate which has shrunken away from alveolar walls in fixing process. In exudate of 2 largest alveoli lie clumps of cells which appear to be cast-off lining cells. These show hyaline-like changes. Interstitium between alveoli is thickly infiltrated with mononuclear cells. (× 180. Hematoxylin and eosin.)

is intact. Inclusion bodies, as described in primary atypical and influenzal pneumonia, are not seen. The pleura is unaltered.

The cellular infiltration of the alveolar and ductal walls described above is almost entirely mononuclear in nature. Cells which resemble plasma cells are in greatest abundance (Figs. 5-7). Also present in large number are cells resembling histiocytes, with larger and paler nuclei. It is usually possible to recognize many intermediary forms with characteristics of both plasma cells and histiocytes, which appear to bridge the gap between the two. Present in much fewer number are cells which resemble fibrocytes, lymphocytes,

large wandering cells and mast cells. Polymorphonuclear leukocytes are usually either absent or present in minimal degree. In only an occasional case, usually one with clinical evidence of secondary infection, is any significant number of polymorphonuclear leukocytes seen.

The alveolar exudate is composed of faintly granular amorphous material, large cast-off alveolar wall lining-cells and hyaline-like masses in variable proportions (Fig. 8). The amorphous material may be faintly eosinophilic, the hyaline-like masses are more strongly so, and neither stains for fibrin. The cast-off alveolar lining-cells, singly or in syncytial clumps, usually lie between the alveolar wall and some amorphous material nearer the center of the lumen. They usually take a rather weak and finely granular fat stain. The eosinophilic hyaline-like material may contain nuclear shadows suggesting origin from alveolar lining cells. It may resemble the hyaline-like membrane often seen in premature infants who die shortly after birth (Fig. 5). However, it is usually not as closely applied to the alveolar wall as in the latter condition. Frequently it lies between cast-off lining cells and amorphous material near the center of the lumen. A few mononuclear cells similar to those present interstitially may be seen in the alveolar exudate. In some cases areas of unusually marked capillary congestion are associated with extravasation of red blood cells into the adjacent tissues and alveolar spaces. This is probably a terminal occurrence.

Histologically the lymph nodes show only a few plasma cells in the sinusoids.

Discussion

The exact nature of the plasma cells and their transition forms, which make up the pronounced interstitial infiltration, has been the subject of investigation.[9, 10] A touch-preparation (made by touching a glass slide to the cut lung of a freshly autopsied patient and stained without the use of fixative) reveals a morphology in these cells which is quite different from those seen in the usual fixed preparations. Undritz,[9] Loustalot[10] and others believe the cells concerned should be termed monocytes rather than plasma cells. It is the present authors' feeling that the young age of the patients plays an important role in the question of cell-type and nomenclature. Newborn and premature infants and foetuses tend to have a different type of cellular response to inflammation than older children and adults. The response, irrespective of cause, tends to be much more lymphocytic and plasmacytic.[11] In addition, the cells involved appear to be of a more primitive order, with greater capacity for variable differentiation. In this sense the plasma cells in the disease under discussion may differ somewhat from plasma cells of older individuals. The authors, therefore, use the term in a broad and inclusive sense. The term "monocyte" would appear equally acceptable if employed in a similarly broad sense.

In addition to the appearance of mononuclear cells with considerable developmental potential, inflammation in the very young tends to be interstitial in location. Thus, in a premature infant an acute bacterial bronchopneumonia will usually cause a more extensive interstitial reaction and a higher mononuclear-polymorphonuclear ratio, both locally and in the blood stream, than it does in older children and adults. Both these tendencies (mononuclear response and interstitial location) are also characteristic of a viral infection, in which category interstitial plasma cell pneumonia is generally believed to lie. The unusual and striking pathology of this disease may then rest, in part, on the coincidence of identical forces, an immaturity factor on the one hand and a possible viral factor on the other. The participation of the alveolar lining-cells in the reaction is striking. While it is true that decrease in alveolar circumference, due to gradual compression, would

alone tend to make these cells appear more prominent, and to pile up to some degree, their histologic appearance often also suggests active proliferation and an increase in size. They are found lying in the alveolar space singly and in sizable groups in various stages of swelling, fat phanerosis and degeneration. An occasional mitotic figure may also be seen.

Also of interest is the almost complete absence of fibroblastic proliferation in the extensive reaction present. Several diseases of known viral origin similarly fail to show a fibroblastic reaction. Finally, there is nothing in the lung to suggest aspiration of milk. Fat droplets and large distended macrophages are not seen.

The lymph nodes appear to be only secondarily involved. A few plasmocytes and wandering cells present in the lymph node sinuses suggest secondary resorption from the lung rather than a primary participation of nodes in the disease.

The present investigators were interested in the question of possible variation in the histologic picture associated with (a) variations in the duration of the disease, (b) in the age of the patient as determined by his birth date, and (c) in his maturity (age based on time of conception as estimated by birth weight, rather than on actual birth date). The effect of duration of the disease could not be studied as the date of onset was so difficult to determine. A careful survey revealed no striking and consistent histologic differences between the youngest and oldest cases when either the actual age (b) or the "maturity age" (c) were considered. Nevertheless there was observed a tendency for the younger and also the less mature cases to show fewer typically mature-looking plasma cells, and a greater proportion which looked like transition forms between plasma cells and histiocytes.

Out of the study has come one surprising finding which the authors are unable to clarify. When comparing the least mature group (eight cases) with the most mature (six cases), all of the former proved to be male, all of the latter female.

The over-all sex distribution of the 35 cases studied was 15 male and 20 female.

Etiology

Numerous reports [1, 7, 8, 12–16] give epidemiologic data supporting the concept that interstitial plasma cell pneumonia is an infectious disease. They indicate a period from 4 to 6 weeks between exposure and the development of that stage of the disease which can be recognized clinically. More than one author has emphasized the origin of cases from one particular ward.[8, 14–16] While cases do occur sporadically and at home, the great majority arise in institutions and as part of a local outbreak of the disease. It is safe to say that today the most commonly held opinion is that the disease is infectious, and probably viral in origin. To date, however, this has not been proved. Assuming an infectious etiology, the evidence favoring a viral etiology rather than a bacterial one is chiefly negative, resting largely on the failure to culture bacterial pathogens, the lack of response to chemotherapy and antibiotics, and the almost complete absence of polymorphonuclear leukocytes except in those cases where secondary infection has occurred.

Other theories of etiology include amniotic fluid aspiration, aspiration of milk, a diffuse neoplasm of the lung such as a variant of the plasmacytoma group, an unrecognized lung irritant or toxin, and the theory that the disease is not specific but represents the manner of response of immature tissue to various infectious or toxic agents. Against these theories it may be said that (1) aspiration of amniotic fluid would lead to difficulty earlier in life and would be associated with hair and epithelial cells which are not seen; (2) aspiration of milk would result in more evidence of fat and large macrophages in the

lung; (3) despite individual cell similarities the over-all histologic picture differs from that of plasmacytomas or myelomas, nor has an abnormal blood protein, such as Bence-Jones protein, been demonstrated; and (4) although the authors, too, believe immature tissues respond somewhat in the manner found in this disease, a different picture nevertheless results when a secondary bacterial bronchopneumonia is superimposed on interstitial plasma cell pneumonia. The pathology of the two diseases is unquestionably quite different in the same individual. Adams[17] also found similar difference in the pathology of bacterial and other forms of pneumonia in infancy.

It has been repeatedly pointed out[6] that loss of maternal antibodies occurs at the time when the disease reaches it peak (2 to 3 months of age), but evidence is lacking that this fact plays any etiologic role. Gamma globulin and blood transfusions have not been of therapeutic value.

Most recently,[18] a parasite Pneumocystis carinii has been suspected. Fungi[19] have also been incriminated in interstitial plasma cell pneumonia but it seems more likely they are secondary invaders.

Hallauer[20] has recently published the results of his attempts to demonstrate a vital causative agent. He reviews the previous work of Weisse[12, 13] and concludes that neither he nor Weisse succeeded in demonstrating beyond doubt the presence of such an agent. The occurrence of a spontaneous interstitial pneumonia in the experimental animals used caused much difficulty and confused the issue of whether or not a virus of human origin was present. Further work along the lines initiated by Hallauer and Weisse is indicated. It should be pointed out that the pneumonia here described, while similar, does differ both pathologically and clinically from luetic pneumonia, from primary pneumonitis as described by Adams,[17] and from the mononuclear pneumonia which Gruenwald recently described[21] in association with sudden death or rapidly fatal illness in infants. The present authors would call attention to the absence of inclusion bodies as seen in atypical pneumonia, to the restriction to the age period 6 weeks to 4 months which is unlike any other pneumonia, to the relative absence of fever and cough present in most other pneumonias, and to the unusually marked degree of the infiltration resulting in almost complete airlessness of the lung at autopsy.

Treatment

There is no therapeutic measure which has proved particularly effective in treating interstitial plasma cell pneumonia. Chemotherapy and antibiotics, including various sulfonamides, penicillin, streptomycin, aureomycin, chloromycetin and terramycin have usually not appeared effective in appreciably changing the course of the disease. Gamma globulin and blood transfusion have failed prophylactically and therapeutically.[1] The same lack of success has followed roentgen and short-wave therapy. If an effective agent is found, the chief problem will be to make a diagnosis early enough to make a therapeutic response possible. Meanwhile supportive measures, especially oxygen and careful nursing, must be relied upon. In view of the apparent importance of humidity in preventing "hyaline membrane" disease of the newborn infant,[22] and the frequent resemblance of the hyaline-like material in the alveoli in the two diseases, high humidification might be useful in treating at least that aspect of interstitial plasma cell pneumonia.

Comment

It is believed that the illness described above is, at the present time, seldom encountered in the United States. In support of this statement are the comments of several experienced

pathologists in different sections of the United States who examined and commented on a typical slide sent to them from one of these recent cases, together with a summary of the history. With one exception, each expressed the opinion that he had not seen the exact counterpart in his own material. One pathologist reported "seeing such a picture a few times in infants on the borderline of viability who survived several weeks or months, but never in larger prematures or full-term infants."

Even in Europe an unusual distribution of the disease seems to be present. While Czechoslovakia, Switzerland, Germany and Austria have all reported numerous cases, no reports from England, Italy and Spain could be found. One Swedish case was reported in 1949[23] and four Danish cases[5, 6] in 1950. The disease is also seen in Finland.[24, 25] An experienced Italian pathologist who sees a good deal of pediatric material reported he had not encountered the condition in Italy.

One is reminded of another affliction of premature infants, namely: retrolental fibroplasia, which has also had a geographic distribution, predominantly in the United States, and until now seldom reported anywhere in Europe. The first Swiss report of this condition[26] appeared during the preparation of this manuscript. Whereas some features of currently employed and possibly geographically limited premature care are suspected of favoring the occurrence of retrolental fibroplasia, a similar explanation does not appear to fit the facts concerning interstitial plasma cell pneumonia. This disease has all the earmarks of an infectious process, and there is no satisfactory hypothesis for the reason for its having acquired geographic limitations, and so largely eschewed the United States.

Summary

An unusual type of infantile pneumonia occurs frequently in certain European countries, but thus far is undescribed in the American literature. It is remarkable clinically in being almost asymptomatic until late in its course, in showing a marked predilection for premature or immature infants, and for being confined to the age period of 6 weeks to 4 months.

Pathologically, it is remarkable for a diffuse interstitial pulmonary infiltration by mononuclear cells which, for the most part, closely resemble plasma cells. An alveolar exudate is also present.

About 22% of patients with clinically recognized cases die of asphyxia. In these cases death appears to be predominantly due to asphyxia.

The most commonly held opinion, in which the authors concur, is that the disease is infectious and probably of viral origin, but as yet there has not been a convincing demonstration of the etiologic agent. Up to the present time no effective therapeutic agent has been found.

Acknowledgment

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SPANISH ABSTRACT

Neumonía Intersticial de "Células Plasmáticas" de los Prematuros y Lactantes Pequeños

Un tipo desusual de neumonía infantil ocurre frecuentemente en ciertos países europeos pero hasta la fecha no ha sido descrita en la literatura americana. Está caracterizada clínicamente, por ser casi asintomática hasta tardíamente en su curso, por mostrar una marcada predilección por prematuros o lactantes inmaduros y por estar limitada al período de edad entre 6 semanas a 4 meses.

Patológicamente se caracteriza por una infiltración pulmonar intersticial difusa de células mononucleares que en su mayor parte se semejan mucho a las células plasmáticas. También se encuentra presente un exudado alveolar.

Cerca del 22% de los casos reconocidos mueren de asfixia.

La opinión mas comunmente sostenida, con la cual los autores estan de acuerdo, es que la enferbedad es infecciosa y probablemente de origen viral, pero aún no ha habido una demostración convincente del agente etiológico. Hasta el momento actual no se ha encontrado agente terapéutico efectivo.

University of California Medical Center

BEHAVIOR CHANGES INDICATING EMOTIONAL TRAUMA IN TONSILLECTOMIZED CHILDREN

Final Report

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DURING the past three years, 140 children have been studied before and after tonsillectomy in an effort to learn whether and under what circumstances this experience is associated with behavior changes which indicate emotional trauma. Since no report of similar work was found in the literature, a method of study was devised which has been described in an earlier report.[1] Briefly, the method consists of conferences by a psychiatric social worker with the mother and the child, during which certain facts about the child's behavior and emotional status were determined. These interviews took place before tonsillectomy, again in the immediate postoperative period, and were repeated after three months. The information obtained in these interviews was studied by a committee made up of three pediatricians, the social worker, the anesthetist. Consulting with the committee were two psychoanalysts, a psychologist and a public health pediatrician.

The children were admitted to one of three Albany hospitals and were operated on by one of three otolaryngologists. Each surgeon operated at each of the hospitals. About half the children were anesthetized by a person with special knowledge and experience in emotional problems, as well as extensive experience and training in anesthesiology. The technic used by this anesthetist is described in a previous paper[2] and consists, briefly, of a preoperative psychologic preparation for the anesthesia experience and a psychologically sound method of administration of the agent.

As might be expected in a new type of research, several problems were encountered. A consideration of these is necessary for the proper evaluation of the findings of the study.

I. Reliability of the Data:

The validity of the information contained in the social worker's report depends upon the intelligence and emotional maturity of the mother, the emotional balance of the child, and the ability of the social worker to evaluate both.

Most parents were intelligent, interested and cooperative. Some mothers were at first ill at ease, thinking that the worker represented a social welfare agency or the hospital financial department. Others considered the interview a "test" in which they answered questions in a way to be sure the child would "pass." Some were reluctant or unable to face the situation, dealt with it lightly, or even flippantly. In almost all cases the parents were better able to cooperate with the social worker after the operation. Their anxiety was relieved, and they were reassured by the worker's interest and objectivity.

The child also was often at first anxious or excited about the experience. While some

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were interested, others seemed to wish to avoid consideration of an occurrence which they feared. In the postoperative interviews, most children were more communicative. Only those who had had a specially painful hospital experience rejected the worker's efforts to be helpful and friendly.

The emotional maturity and balance of the social worker is of prime importance in the matter of obtaining reliable data. The worker must be free from bias, overidentification, and from any emotional conflict which would tend to interfere with objectivity.

II. "Control" Problem:

At the beginning, the investigation was planned as a controlled study. In various phases, however, this was discovered to be impossible.

A. Interview.—The social worker, being trained as all social workers are to give service, found it impossible to secure the cooperation of parents and children in a questionnaire type of interview. Only when the worker could offer practical help, explanation or reassurance could the parent or the child give real cooperation and information. Thus the interviews became almost identical in all cases.

B. Treatment in the Pediatric Ward.—It was planned that the treatment the child received in the ward could be controlled by having half of the children operated upon in Albany Hospital where the pediatric staff and nurses recognize the importance of the emotional aspects of the hospital experience. The other half were to have been admitted to other hospitals where such factors are not stressed. However, the surgeons who cooperated in the study preferred to use Albany Hospital, so that a smaller number of the cases are from other hospitals. Obviously, when what would otherwise have been "control" patients were admitted to Albany Hospital, they could not be treated differently from the other children.

C. Anesthesia Procedure.—In the matter of the anesthesia experience itself, a fair approximation of a "control" grouping was made. Even here, however, some difficulty was encountered. Other anesthetists, working in association with the one engaged in the study, soon began to modify their technics in the direction of more psychologically sound practices. Some of the children, therefore, in one of the contrast groups were anesthetized by a method somewhat similar to that used by the "study" anesthetist.

III. Problem of Compiling and Reporting the Data:

Two consultants to the committee, accustomed to the statistical method of compiling and reporting results in medical research, felt that the findings in this study could and should be so reported. Attempts in this direction met with early failure, in the following respects:

A. The sample, being made up of patients of certain surgeons, is thus somewhat restricted in the matter of economic and social status and in race. The nature of the information required imposes limitations of intelligence, emotional integrity and willingness to cooperate on the part of the parents.

B. The nature of the material under consideration was such that numerical evaluation of the findings was often impossible. Only in objective signs, such as nightmares or bedwetting, could there be any mathematic comparison of the findings before and after the hospital experience. The real significance even of numerically demonstrable behavior change could only have been discerned by psychiatric examination of the child.

C. The unlimited number of variables which is present in any consideration of emotional problems made it impossible to state categorically that any one observation was the undisputed result of any single factor.

This study has for its purpose the observation of pre- and postoperative behavior pat-

terns, in an effort to determine whether changes occur which might indicate the presence of emotional trauma associated with the hospital experience.

A change of behavior following operation may be due either to physical or emotional factors. Since physical factors (sore throat, dehydration, changes in upper respiratory patency, etc.) are so pronounced in the immediate postoperative period, observations made at this time were not taken as criteria. The changes present after three months may also be of mixed origin. A child who is relieved of serious upper respiratory obstruction or infection would be likely to behave differently. This factor was, however, common to all the children, since all the tonsillectomies were done for real local pathology. Difference in behavior response at three months, when the physical factors were common to all cases, may be taken as an indication of difference in emotional response.

In this study, emotional trauma is considered to be associated with an increase in any of the negative feelings: anxiety, suspiciousness, resentment, hostility, inadequacy, insecurity or a need to retaliate.[3] Children express their feelings in their behavior. The following behavior traits were taken as criteria because they are easy for the mother to observe and evaluate, and because they supply abundant evidence of the child's emotional status.

A. Appetite and eating habits: A child may express his resentment, his need to control the mother or a need to cling to the mother by eating less willingly, demanding to be fed, wanting only liquids, or becoming generally "finicky."

B. Dependency: A child's having to be dressed or fed, or otherwise being less able to care for himself is regressive behavior usually indicating feelings of inadequacy or insecurity, or a need to control the mother. A child often clings closer to his mother when he is suspicious or uncertain of her love.

C. Disposition: Overt expression of retaliatory feelings, resentment or hostility may be directed against the parent because the child considers the parent to have been a party to an unpleasant experience. Or these feelings may be projected to the family, being originally stimulated by someone at the hospital.

D. Sleep habits: A child who has felt seriously threatened by the anesthesia may become rebellious about going to bed or fight falling asleep even at nap time. Nightmares and other sleep disturbances are indications of fearful feelings which are not expressed during consciousness.

E. Mannerisms: Increased or new self-comforting devices or compulsive behavior may indicate regression with evidence of unconscious anxiety.

The authors realize fully that emotional trauma can occur without overt evidence in the form of behavior changes. Nothing short of psychoanalytic study could determine whether trauma has occurred in these children as a result of the hospital experience. Concrete evidence might be years in becoming manifest.

This study shows only that certain children were acting out conscious and unconscious negative feelings three months after their tonsillectomy. Whether any of these children (or of the others, for that matter) were lastingly traumatized could only be determined by further study.

Findings

In more than half of the 140 children the behavior either showed no change of any kind, or was improved. A second group, about 30%, showed a mixed reaction, with improvement in some traits and disturbance in others. In most of these the improvement was predominant, so that the mother considered the child's behavior to be essentially better. In

a few cases the disturbances outweighed any improvement, and the child was considered to have reacted negatively to the experience. The remaining children showed consistent deterioration in behavior. In some of these the change was slight and occurred in only one trait. Neither the mother nor the social worker considered these to be adversely affected.

A method of scoring the reactions was devised which makes use of a profile system. Figure 1 shows a sample card on which is entered the response in each behavior category, and the resulting index.

Sample Code Card

Case 32S	Better=1	No change=2	Worse=3
A. Eating habits	X		
B. Dependence		X	
C. Temper			X
D. Sleep habits		X	
E. Mannerisms		X	
Profile Number—12322 Profile Index —10			

FIGURE 1

Applying this index to the groups described above, the children who showed only improved behavior had indices of 9 or less. A child with no change would have an index of 10. One who showed deterioration in one category would have an index of 11. In the case of a mixed response, a child whose disturbance was compensated for by improvement, as in the sample, the profile would be 10. Where the improvement outweighed the disturbance, the index would be 9 or less. If the deterioration was predominant, the index would be 11 or more.

All case histories were reviewed in detail to make sure that the index was a fair evaluation of the response. In doing this it was found that no child with an index of 11 or below showed enough change in behavior to be considered adversely affected. In 13 cases the index was 12 or above. In all these the case history also indicates behavior changes which suggest the presence of emotional trauma. Examination of these cases will provide information about the factors involved in this negative response.

Among those children operated on at Albany Hospital and anesthetized by the special method referred to above, four are found in this high index group. The ratio of high index in this group is 1:19. In the cases treated at Albany Hospital without special anesthesia, the ratio of high index is 1:8. Among the cases treated at other hospitals this ratio is 1:5. If we think of these three groups as representing different "degrees" of psychologic consideration in treating the child, the ratio of high profile index seems related inversely to the "degree" of such consideration.

In order to learn whether other traumatic experience exerted influence in the reaction to this hospital experience itself, the personal history of each child was evaluated with reference to potentially traumatic incidents or situations. These factors were grouped in the following manner.

I. Serious threat to the integrity of the home, such as known serious emotional inadequacy in a parent or serious marital disturbance.

II. Previous potentially traumatic experience, such as early separation from the mother including hospitalization, death of parent or sibling or noticeable congenital abnormality.

III. Any aspect of this hospitalization which might add to the possibility of emotional trauma, such as excessive treatments, absence of the parent or unwise handling by hospital personnel.

In cases where none or only one of the above factors was present, one child in 26 is found in the high index group. Where there are 2 or 3 factors the ratio is 1:6.7, or 4 times as high. In this age group, previous experience with emotional trauma seems to be a handicap rather than a conditioning for the hospital experience.

With specific reference to unnecessary avoidable trauma in the hospital, it is found that where such occurred, one child in 8 had a high profile index. Where there is no evidence of such trauma this ratio is 1:14.

The children ranged from 3 to 8 years of age. Not much difference is found in the incidence of high profile index among those 4 years or more old. The three year olds show a higher incidence of minor behavior disturbances, although none are found in the high profile group. In view of the findings of Levy,[4] we would expect to find more serious disturbances among the younger children. On the other hand, traumatic effects may be slower to appear in the younger ones.

Summary

A study of 140 children was made before and after tonsillectomy to determine the incidence of behavior changes indicative of emotional trauma.

A method of procedure, presented in earlier papers, is briefly described. The difficulties and problems of this type of research are evaluated. The limitations of the research method in proving the presence or absence of emotional trauma are acknowledged.

Findings were: 1. Thirteen children presented behavior changes indicative of emotional trauma. 2. Children treated with consideration for emotional factors gave less evidence of trauma. 3. Children who had suffered previous emotional trauma reacted less well to this experience. 4. Younger children showed more but milder adverse behavior changes. 5. The large majority, 91%, seemed either benefited by or were scarcely affected by the experience.

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Spanish Abstract

Cambios de Conducta que Indican Traumatismo Emocional en Niños Amigdalectomizados

Se estudiaron 140 niños antes y después de la amigdalectomía para observar la conducta pre y post operatoria y determinar los cambios realizados con la experiencia quirúrgica y hospitalaria, indicativos de traumatismos emocionales. Los cambios se pueden deber a factores físicos y emotivos; puesto que los primeros son muy acentuados en los primeros días después de la operación, las

observaciones de este período no se tomaron como criterio. Los cambios a los tres meses también pueden ser de origen mixto; al eliminar la infección y la obstrucción respiratoria de los niños (factor físico), éstos se comportarían de manera diferente; y como este factor fue común a todos los pacientes, los cambios observados pueden considerarse como indicativos de diferencias en las respuestas emotivas. Se tomaron los siguientes sentimientos como manifestaciones de trauma emocional: ansiedad, resentimiento, inadaptibilidad e inseguridad, traducidos en los cambios de apetito y hábitos de comer, sentido de dependencia, modo de ser, sueño y manías.

Sólo algunos niños presentaron tres meses después de la operación manifestaciones psíquicas negativas, conciente o inconcientemente. Tres niños mostraron cambios de conducta; los tratados con consideración y comprensión dieron menos muestras de traumatismo; los niños con traumatismos previos emocionales se comportaron peor; en términos generales los niños más pequeños mostraron más cambios diversos de conducta, aunque en forma ligera; y por último, la mayoría de los niños observados (91%) no fueron afectados por la experiencia o bien fueron aparentemente beneficiados.

48 Willett Street

EFFECTS OF HYDRAZINOPHTHALAZINE (APRESOLINE®) ON BLOOD PRESSURE AND RENAL FUNCTION IN CHILDREN WITH ACUTE NEPHRITIS

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HYPERTENSION is a common, and at times serious, complication of acute glomerulonephritis in children. The factor or factors responsible for the transient episodes of hypertension in acute nephritis have not as yet been defined. The treatment of hypertension in acute nephritis is largely symptomatic. Consequently, it is important to be certain that agents capable of lowering elevated blood pressure in acute nephritis do so without adversely affecting either renal function or the clinical course of the disease. A potent new hypotensive agent, C 5968, 1-hydrazinophthalazine (apresoline®*), has recently become available for clinical use. This agent has the unusual pharmacologic property of increasing renal and femoral blood flow in the dog and rabbit while lowering blood pressure,[1] an effect not produced by most circulatory depressants. This effect of apresoline® on renal blood flow in man was first demonstrated by Reubi.[1] This drug has been found to be therapeutically useful in the management of patients with essential hypertension.[2,3] The use of the drug is not without undesirable side effects, however, and serious hypotensive reactions have been described.[4] The following report concerns the clinical evaluation of apresoline® in terms of its effects (1) on blood pressure and course of illness and (2) on renal function in a small group of children with acute glomerulonephritis associated with hypertension.

Methods and Materials

Clinical material consisted of patients admitted to the wards of the Children's Hospital of Philadelphia with one exception, Patient J.N., who was observed in another hospital. Measurements of renal function were performed by standard clearance technics. Inulin clearance was used as a measure of glomerular filtration rate (GFR) and para-aminohippurate clearance was used as a measure of renal plasma flow (RPF). An indwelling catheter was used for urine collections, and a motor-driven injection pump was used to maintain a constant rate of infusion of inulin and para-aminohippurate. All blood pressure determinations were made by the auscultatory method.

Results

I. Clinical Evaluation of Antihypertensive Effect of Apresoline®

Observations have been made of the response of blood pressure in seven children with acute nephritis associated with hypertension who received apresoline® during their hypertensive episode, and in two patients with persistent hypertension associated with chronic renal disease.

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* Apresoline® used in this study was generously supplied by Ciba Pharmaceutical Co.

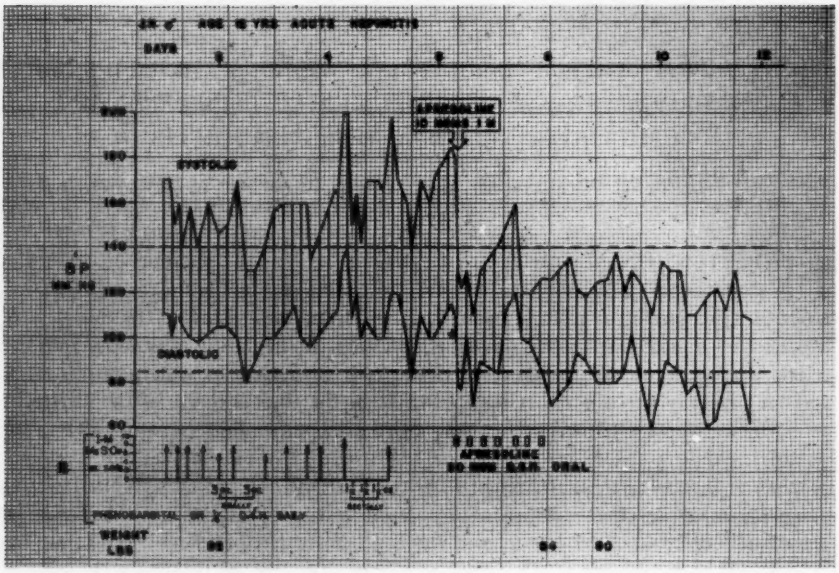

CHART 1. Changes in blood pressure in child with acute nephritis, and hypertension in relationship to administration of apresoline®. Limits of normotensive blood pressure are indicated by dotted lines.

A. Response of Hypertension in Children with Acute Nephritis: Apresoline® was given to seven children with acute nephritis, and associated hypertension. A parenteral dose of 0.2 to 0.25 mg./kg. was found to be effective in inducing temporary hypotension. In the majority of instances, the parenteral administration of apresoline® resulted in a prompt fall in both systolic and diastolic pressure within 30 minutes after injection. The fall in mean pressure ranged from 20 to 40 mm.Hg. The hypotension was regularly accompanied by tachycardia of some degree, and both effects persisted for 2 to 4 hours on the average. Side effects included nausea and vomiting, orthostatic hypotension, dizziness and some tachypnea. Subjectively, there was relief of apprehension and headache when present.

Oral administration following the initial parenteral injection was employed in four instances, oral dosage ranging from 50 to 200 mg. daily. Oral therapy was continued until blood pressure had returned to normotensive levels. The longest period of treatment was three weeks. There was no return of hypertension following withdrawal of the drug. An example of such a symptomatic response is shown diagrammatically in chart 1. In this patient parenteral $MgSO_4$ and sedation had been without significant effect on blood pressure. Within 20 minutes after the intramuscular injection of apresoline® 10 mg., a fall in systolic and diastolic blood pressure began. The actual fall in B. P. was from 180/115 to 130/80 in one hour, and it remained in this lower range for 12 hours. Oral administration started at the time of the first injection was continued at six hour intervals for 18 hours, by which time blood pressure had returned to essentially normal levels. Following the cessation of oral medication, there was no return of hypertension. The disappearance of hypertension in this instance was in all probability related to the coincident occurrence of spontaneous improvement with loss of edema (indicated by the decreases in weight, chart 1)

during the period of apresoline® therapy. It is clearly evident, nonetheless, that apresoline® did favorably modify the hypertension while it existed.

Essentially similar responses were observed in the three other children. Thus a total of 4 of the 7 children with hypertension and acute nephritis had an apparently favorable clinical response to apresoline®. Of the remaining three children, one received apresoline® 0.2 mg./kg. intramuscularly 4 times a day for 5 days, and temporary hypotension was regularly induced. In another patient, no fall in blood pressure occurred on the standard parenteral dose, 0.2 mg./kg. When the parenteral dose was doubled, the patient vomited, complained of headache, and developed a temporary tachycardia without fall in blood pressure. The third patient, in whom a single parenteral injection of apresoline® produced a prompt fall in blood pressure, developed a severe bout of vomiting, associated with dizziness and oliguria at a later date, when given two 50 mg. oral doses of apresoline®. These symptoms persisted for 36 hours and were accompanied by a hypotensive response of equal duration.

The fact that the five children treated for prolonged periods with apresoline® had abatement of hypertension and clearing of edema while receiving the drug would suggest that the consequent lowering of blood pressure did not adversely affect the course of glomerulonephritis in these subjects.

B. Response of Hypertension in Chronic Nephritis: The effect of apresoline® in the two patients with chronic renal disease and persistent hypertension was much less impressive than that observed in acute nephritis. Parenteral apresoline® would induce a prompt but short-lived fall in blood pressure, though less regularly than in patients with acute nephritis and hypertension. Orally administered apresoline® did not maintain their blood pressure at normotensive levels though a decrease in mean daily pressure of 10 to 15 mm.Hg was observed. It is of interest that parenteral apresoline® was effective in temporarily inducing hypotension in one of these patients during a hypertensive encephalopathic crisis, during which parenteral magnesium sulfate (0.2 cc. 50% soln/kg.) was without effect.

II. Effect of Apresoline® on Renal Function

The consideration of the effects of this drug on renal function in such subjects is of greatest importance. In an attempt to gain information on this point, the authors observed its effect on renal function in seven children in varying stages of acute nephritis. All but 2 (M.D. and H.H.) of the 7 were members of the group described above. Clinical data are shown on table 1.

A. Method of Study. After three 15 to 20 minute control clearance periods had been

TABLE 1

CLINICAL DATA OF SUBJECTS AT TIME OF RENAL FUNCTION STUDY

Pt.	Age	Sex	Duration of Disease	Hematuria	B.P. mm.Hg
M.D.	7 yr.	M	18 days	0	98/60
P.K.	3 yr.	F	30 days	+	100/58
A.W.	11 yr.	F	23 days	Gross	130/84
J.S.	12 yr.	F	32 days	Gross	160/120
K.T.	5 yr.	F	10 days	+	120/80
F.M.	8 yr.	F	43 days	Gross	122/72
H.H.	5 yr.	M	23 days	Gross	150/110

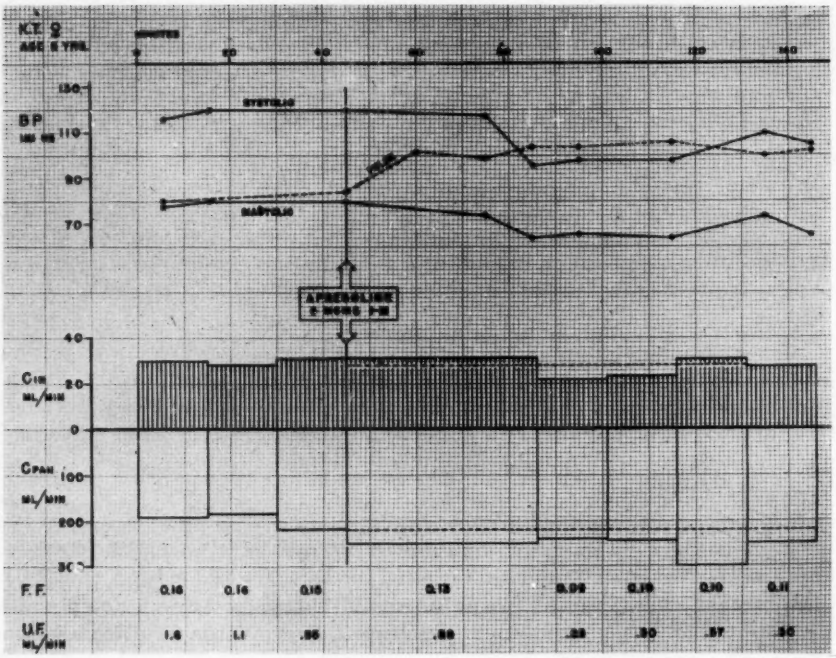

CHART 2. Changes observed in renal function in child with acute nephritis accompanying fall in blood pressure induced by apresoline®. Glomerular filtration rate shown as C_{IN}, renal plasma flow shown as C_{PAH}. Control value indicated by extended dotted line.

measured, the patients received a single parenteral injection of apresoline®. The authors' experience had shown that the maximum effect of parenteral apresoline® on blood pressure was obtained 40 to 60 minutes after the injection, and this persisted for 40 to 60 minutes followed by a gradual return of blood pressure to pre-injection levels. Accordingly, clearance observations were continued for a minimum of 90 minutes and up to as long as 120 minutes after injection.

B. Results: The changes in renal function were variable, and no relationship was apparent between them and the degree of systemic vasodilatation (as judged by the observed fall in blood pressure) or the dosage of apresoline®. To demonstrate extremes in variations, two responses are presented in diagrammatic form (charts 2 and 3). In Patient K.T. (chart 2) a fall in blood pressure occurred associated with an increase in renal plasma flow (RPF) (shown as C_{PAH}). Glomerular filtration rate (GFR) (shown in C_{IN}) was decreased during the period of maximal hypotension, but otherwise unchanged. In contrast (as shown in chart 3) though only a slight fall in systemic blood pressure occurred in Patient A.W., a marked reduction in both RPF and GFR was observed following administration of apresoline®. In the first instance (chart 2) the increase in renal plasma flow would indicate that some renal vasodilatation did accompany the lowering of systemic blood pressure* as has been reported in man by others,[1,2] while the opposite change in

* The limitations in use of C_{PAH} as a measure of renal plasma flow (RPF) in the diseased kidney[5,6] is acknowledged by the authors. In these acute experiments, they feel justified, however, in in-

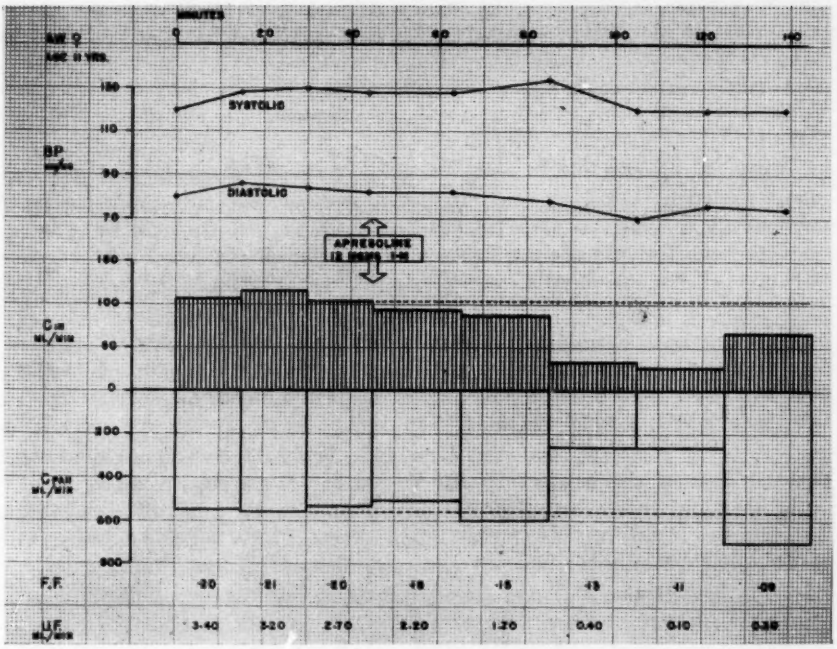

CHART 3. Marked depression of renal function with only slight change in blood pressure observed following administration of apresoline® to child with acute nephritis. Glomerular filtration rate shown as C_{IN} and renal plasma flow shown as C_{PAH}, control value indicated by extended dotted line.

renal plasma flow (indicating renal vasoconstriction) occurred in Patient A.W. with only a slight change in arterial blood pressure. This severe temporary depression in GFR and RPF (in A.W.) could well represent in part an unusual untoward reaction of the patient to either the drug or the procedures. Examination of the findings in all seven subjects, however reveals certain similarities in the observed alterations in the pattern of renal hemodynamics, even though the change in absolute value of GFR and RPF was variable. Pertinent data is presented in summary form in table 2. The control value represents the average of three 15 minute clearance periods, and the one hour value represents the average of two 20 minute clearance periods from 40 to 80 minutes after injection. The data presented in this way show the maximum effects observed in these patients following a single injection of the drug (table 2).

A variable decrease in GFR (C_{IN} decreased from -19% to -73%) was observed in 5 of the 7 observations during the period of maximal response to parenteral apresoline®. It is interesting to note that in the two instances (M.D. and P.K.) in which there was no fall in blood pressure, GFR was unchanged and RPF increased. In the five subjects in whom a fall in mean arterial pressure (Pm, table 2) occurred the direction of change in RPF was variable. An increase was observed in only one (K.T.), no change in 2 (F.M.

terpreting the changes in C_{IN} and C_{PAH} as changes in GFR and RPF, respectively, and as indicating the pattern of renal hemodynamic alteration even though the exact degree of integrity of tubular transport of PAH and, consequently, the true renal plasma flow is unknown.

TABLE 2

CHANGES IN RENAL FUNCTION INDUCED BY APRESOLINE® IN CHILDREN WITH ACUTE GLOMERULONEPHRITIS

Pt.	Apresoline® mg./kg.	Response					
		Period	Pm†	GFR‡	RPF§	F.F.‖	UF¶
M.D.	.15 mg.	Control	69	103.5	278	.37	1.24
		+1 hr.*	84	112.0	374	.30	.49
P.K.	.15 mg.	Control	72	70.2	364	.19	.31
		+1 hr.	73	68.6	418	.16	.36
A.W.	.2 mg.	Control	99	139.0	700	.20	3.1
		+1 hr.	87	39.8	326	.10	.25
J.S.	.2 mg.	Control	133	23.2	111	.21	1.9
		+1 hr.	105	12.2	92.5	.13	.36
K.T.	.25 mg.	Control	93	70.3	459	.15	.93
		+1 hr.	74	52.9	566	.10	.29
F.M.	.25 mg.	Control	89	39.8	416	.10	1.7
		+1 hr.	73	26.6	378	.07	.36
H.H.	.4 mg.	Control	123	47.2	438	.11	1.3
		+1 hr.	92	39.8	443	.09	.20

* +1 hr. = 1 Hour Post Injection (see text).
† Pm = Mean Arterial BP, mm. Hg
‡ GFR = C_{IN} ml./min. corrected to 1.73 m.² S.A.
§ RPF = C_{PAH} ml./min. corrected to 1.73 m.² S.A.
‖ F.F. = Filtration Fraction C_{IN}/C_{PAH}.
¶ UF = Urine flow ml./min.

and H.H.) and a decrease in 2 (A.W. and J.S.). Filtration fraction (F.F.), however, was consistently decreased, even when RPF was decreased. A decrease in urine flow (U.F.) was observed in 6 of the 7 subjects. In every instance in which some fall in blood pressure was observed following administration of apresoline® (the primary physiologic alteration of interest in the clinical evaluation of this drug) a decrease in GFR and urine flow was also observed.

DISCUSSION

It would appear that apresoline® can induce a significant temporary drop in blood pressure in children with hypertension occurring as a complication of acute nephritis. If this agent is to be of therapeutic value, it is important to be aware of any adverse effects on renal function. These observations would seem to demonstrate that a variable temporary reduction in glomerular filtration rate and urine flow accompanies the hypotension induced by apresoline® in children with acute nephritis. A fall in systemic arterial blood pressure is usually accompanied by a compensatory decrease in renal vascular resistance (arteriolar tone) since there would otherwise be a proportional reduction in RPF and GFR. Even

though RPF was not regularly increased, the fact that decreases were observed in only 2 of the 5 instances in which blood pressure was lowered would indicate that some dilatation of the renal afferent arteriole occurred in three of these subjects during the period of temporary hypotension, since changes in RPF reciprocally reflect changes of afferent arteriolar tone. Changes in filtration fraction, however, directly reflect changes in efferent arteriolar tone. The fact that F.F. consistently decreased following administration of apresoline® irrespective of the effect on blood pressure or RPF is of special interest. As mentioned above, renal vasodilatation of both afferent and efferent arterioles (demonstrated by an increase in RPF, no change in GFR and, hence, a decrease in filtration fraction) has been induced in man by parenteral administration of apresoline®.[1] The consistent decrease in filtration fraction observed in these children with acute nephritis following apresoline® could be interpreted as indicating that some degree of efferent renal arteriolar dilatation (relative or absolute) was induced in all subjects even though the dominant change in two instances where RPF decreased was afferent renal arteriolar vasoconstriction. One can speculate that such an alteration in renal hemodynamics in these subjects could, in light of present concepts of the pathologic physiology of acute glomerulonephritis, contribute to a reduction of glomerular filtration rate.

In the studies of Earle et al.,[7] the commonest pattern found in renal function studies in acute glomerulonephritis was a greater reduction in GFR than in RPF, with a low filtration fraction. The major renal functional derangement in nephritis would appear to be a decrease in permeability of the glomerulus rather than obstruction of the flow of blood through the glomerulus.[7] In this circumstance, renal vasodilatation associated with a reduction in efferent arteriolar tone, and a fall in systemic blood pressure may not be desirable. Such vasodilatation could result in a further reduction in filtration rate by lowering filtration pressure, and thus exaggerate the functional derangement occurring in the kidney with acute nephritis. An explanation of the significance of the observed depression in urine flow cannot be given at this time. The fact that the low rate of urine flow persisted after the return of the GFR to normal (charts 2 and 3) would indicate that it was not simply the result of the reduction in GFR, but represented in part an antidiuretic effect of apresoline® on tubular water excretion mechanisms.

In summary, even though apresoline® can induce a fall in blood pressure in patients with acute glomerulonephritis and hypertension, it may also temporarily depress renal excretory function. Further study will be needed to establish the validity of these findings. Until a final answer is forthcoming, it would appear the apresoline® can have an adverse effect on renal function in children with acute nephritis.

The clinical use of this potent hypotensive agent would, consequently, appear to be limited to situations in which more critical complications of uncontrolled hypertension appear to clearly outweigh the potential dangers of this form of therapy.

Conclusions

The response of hypertension occurring in acute nephritis in children to apresoline® has been studied. Significant temporary reductions in elevated blood pressure were produced by parenteral and oral apresoline® in 5 of 7 children with acute nephritis. The effect of this agent in two patients with hypertension and chronic renal disease was less impressive.

Studies of changes in renal function following parenteral administration of apresoline® were made in seven children with acute nephritis. Significant temporary depressions of the glomerular filtration rate and urine flow were observed in every instance in which apresoline® induced a fall in systemic blood pressure.

Apresoline® did not regularly induce an increase in renal plasma flow in these subjects. Changes in renal plasma flow were variable, and even decreases were observed. Even though apresoline® can induce a fall in blood pressure in children with hypertension and acute nephritis, this response may be associated with a temporary depression in renal excretory function.

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Spanish Abstract

Efectos de un Depresor Vascular (Apresolina®) Sobre la Presión Sanguínea y la Función Renal en Niños con Nefritis Aguda

Siendo la hipertensión una complicación frecuente y en ocasiones muy grave de la glomerulonefritis aguda de los niños y no conociéndose claramente los factores responsables, el tratamiento es fundamentalmente sintomático y debe realizarse con agentes que al reducirla no afecten la función renal o el curso del padecimiento. Este estudio valoriza la acción de un nuevo agente hipotensivo (C-5968, I-Hidrocinoftalacina Ciba, con nombre comercial de Apresolina), estudiando sus efectos sobre la presión sanguínea, el curso del padecimiento y la función renal en un pequeño número de niños con glomerulonefritis aguda con hipertensión.

1. Valoración Clínica del efecto hipotensor.

(a) Respuesta de la hipertensión en niños con nefritis aguda: Esta droga se les dió a 7 niños con nefritis aguda, por vía parenteral en dosis inicial de 0.2 a 0.25 miligramos por kilo de peso; se observó baja de presión 30 minutos después, que persistió de dos a cuatro horas. La administración oral después de la dosis inicial se continuó en 4 casos, a razón de 50 a 200 miligramos por día y continuándose hasta tener presiones sanguíneas normales; al suspender la droga no se observó hipertensión. A los tres niños restantes se les continuó con 0.2 miligramos por kilo de peso cada seis hora, por vía intramuscular, habiéndose suspendido por efectos desagradables generales atribuíbles a la droga, en dos de ellos, mientras que al otro se le dió sólo por cinco días con los resultados observados cuando se administró por vía oral.

(b) Respuesta a la hipertensión en la nefritis crónica: La respuesta en dos casos estudiados fué mucho menos efectiva pues la vía parenteral produjo una baja en la presión de corta duración, y la vía oral tan sólo ligera pero sin llegar a lo normal.

2 Efecto de la apresolina en la función renal.

Los cambios en la función renal fueron variables en grado, en los siete niños con nefritis aguda; todos mostraron una depresión temporal de la filtracion glomerular y de la secreción urinaria así como alteraciones variables también, en la circulación plasmático renal.

En resumen, los autores obtuvieron descenso de la presión sanguínea, pero al mismo tiempo depresión temporal en la función renal, en los niños nefríticos agudos con hipertensión, hechos que requieren mayor estudio para valorar debidamente la utilidad de la apresolina.

1740 Bainbridge Street

CHEMOTHERAPY OF MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS

A Public Health Service Cooperative Investigation
Washington, D.C.

EARLY trials of streptomycin treatment of miliary tuberculosis and tuberculous meningitis revealed the significant fact that these diseases need no longer be almost invariably fatal. However, a number of serious problems remained unsolved, and others had been created. Although streptomycin was extremely effective in the treatment of miliary disease, it did not eliminate the appearance of meningitis among some miliary patients. In tuberculous meningitis, not only did the mortality rate remain disturbingly high, but there was a high frequency of crippling sequelae among the "arrested" patients. Relapse sometimes occurred many months after arrest seemed established. The healing process itself was recognized as one of the principal obstacles to complete recovery, since exudate surrounding the brain stem led to obstructive hydrocephalus in many patients whose infections had been brought partially under control.

Hope of improving upon the results obtained with streptomycin centered around the adjuvant use of other tuberculostatic agents. Lincoln[1] was obtaining excellent results in miliary tuberculosis with promizole®, and para-aminosalicylic acid had already shown *in vitro* a capacity to retard the emergence of streptomycin-resistant tubercle bacilli.

Against this background, the United States Public Health Service, Federal Security Agency, early in 1948 initiated a study of the use of promizole® and para-aminosalicylic acid in combination with streptomycin for childhood miliary and meningeal tuberculosis. This was a part of the streptomycin evaluation program of the Field Research Branch, Division of Chronic Disease and Tuberculosis. Investigators from seven pediatric centers with grants from the National Institutes of Health cooperated under a standard protocol.

Participating investigators and hospitals were as follows:

Babies Hospital, New York City, Dr. Hattie E. Alexander and Dr. Walter Damrosch.

North Reading State Sanatorium, North Reading, Mass., and The Children's Hospital, Boston, Dr. William Berenberg.

The Johns Hopkins Hospital, Baltimore, Dr. Janet Hardy.

Temple University Hospital and St. Christopher's Hospital for Children, Philadelphia, Dr. Robert H. High.

National Jewish Hospital, Denver, Dr. Allan Hurst.

Charity Hospital and Tulane Medical School, New Orleans, Dr. Ralph V. Platou.

Flower and Fifth Avenue Hospitals, New York City, Dr. Lawrence B. Slobody.

Uniform clinical reports for each patient were submitted to the central office at predetermined intervals until death or for the duration of the study, and detailed autopsy reports were obtained whenever possible.

This report was prepared for the investigative group by Mrs. Laura R. Rosen, M.A., Dr. Philip A. Kilbourne, and Mrs. Shirley Ferebee representing the Public Health Service, Department of Health, Education, and Welfare in the medical and statistical coordination of the study, and Dr. Robert H. High, medical consultant.

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TABLE 1

COMPARISON OF LOW DOSAGE SCHEME AND HIGH DOSAGE SCHEME

Drug	Low dosage scheme (April 1948)			High dosage scheme (November 1948)		
	Dose	Frequency	Duration	Dose	Frequency	Duration
Intramuscular streptomycin	20 mg./kg. body wt.	Every 12 hr.	84 injections	50 mg./kg. body wt. (single dose not to exceed 1.5 gm.)	Every 12 hr.	84 injections given in courses of 6 wk. each, followed by 10 day rest. Any number of courses allowed
Intrathecal streptomycin (for meningeal patients only)	2.0 mg./kg. body wt.	Daily for 4 days, then on alternate days	Minimum period, 4 wk.; if CSF sugar not returned to normal at 4 wk., continued until total of 6 wk. has elapsed	50 mg. for any patient regardless of wt.	Daily for 4 days, then on alternate days	Given in courses of 6 wk. each, followed by 10 day rest. Courses to run concurrently with courses of intramuscular treatment
PAS (given orally)	0.2 gm./kg. body wt.	To be divided each day into 4 doses at intervals of 6 hr.	Beginning with 8th day of streptomycin treatment and continuing 6 mo.	0.2 gm./kg. body wt.	To be divided each day into 3 doses at intervals of 8 hr.	Given continuously without interruption until 4½ mo. had elapsed after completion of streptomycin therapy
Promizole ® (given orally for Regimen I patients only)	0.5 to 1 gm. daily at outset, increasing until blood level maintained at 2–3 mg./100 cc.	Daily	6 mo.	0.5 gm. increasing as tolerated to 1.0 gm. for children under 6 mo. of age and to maximum of 2.0 gm. for children 6 mo. or older	Daily	Given continuously without interruption until 4½ mo. had elapsed after completion of streptomycin therapy

DRUG REGIMENS

Under the plan of study, assignment of individual patients to one of two regimens was made in the central office according to a strict system of chance allocation. Each patient continued on this regimen as long as any chemotherapy was indicated. Streptomycin and para-aminosalicylic acid were used in both regimens, but promizole® only in Regimen I. Streptomycin was used intrathecally only in the meningeal patients.

Streptomycin was given in six week courses, as many as indicated by the patient's condition, with a 10 day "no streptomycin" period between courses. Para-aminosalicylic acid and promizole® were continued 4½ months after the completion of the last course of streptomycin.

During the first seven months of study, the intramuscular dose of streptomycin was 20 mg./kg. body weight at 12 hour intervals and the intrathecal dose 2.0 mg./kg. body weight daily for four days, then on alternate days. The early program is subsequently referred to as the "low" dosage scheme.

In November 1948 the 12 hour intramuscular dose of streptomycin was raised to 50 mg./kg. body weight and the daily intrathecal dose was changed to 50 mg. regardless of weight. At this time the dose of promizole® which originally was increased from 0.5 mg. daily until the blood level was maintained at 2-3 mg./100 cc. was changed to be increased as tolerated to a maximum of 1.0 gm. daily for children under 6 months of

age and 2.0 gm. daily for older children. The daily dose of 0.2 gm./kg. body weight of para-aminosalicylic acid remained substantially the same throughout. The later program is subsequently referred to as the "high" dosage scheme. Table 1 lists the details of the two dosage schemes.

MATERIAL

Infants and children were admitted to the study between April 1, 1948, and March 31, 1950. Section I of this report is concerned with 32 patients who had only miliary tuberculosis on admission to the study. Section II describes 93 patients with tuberculous meningitis, 23 of whom also had miliary tuberculosis. The report is based on the results of 12 months of observation for each patient, while an addendum to each section summarizes the condition of patients at follow-up in April, 1952.

I. MILIARY TUBERCULOSIS

Diagnostic Criteria.—Chest roentgenograms taken at the start of treatment for 32 infants and children were read independently in the central office by 3 qualified persons. Hematogenous dissemination consistent with a diagnosis of miliary tuberculosis was reported by the 3 viewers for all in the group. For 30 patients, the RGs revealed active pulmonary involvement in addition to the miliary dissemination and for one, a calcified lesion.

All 32 children had positive intradermal tuberculin reactions. The diagnosis of tuberculosis was further substantiated by positive cultures for M. tuberculosis in 22 and by other means in 4. The remaining 6 were under 1 yr. of age and had definite household exposure to an open case of pulmonary tuberculosis. At the time of admission to the study all of the children were acutely ill.

Initial Comparability of Regimen and Dosage Groups.—The original plan of study were based upon estimates of patients with miliary tuberculosis available from the participating clinical centers during the next year. The total actually submitted proved to be much lower than the estimates. Although the admission period was extended to 2 yr., the number of children with miliary tuberculosis was, for purposes of this study only, disappointingly small. Consequently, the composition of the 2 regimen groups, while comparable with respect to many of the important variables, is not as similar for some items as would have been expected from the randomization of a larger series of patients.

The total study group was composed largely of infants under 1 yr. of age. The regimen groups are similar as to age composition, but in the dosage subgroups, fewer infants received the low dose. The entire series was about equally divided between boys and girls, and between whites and nonwhites of whom all except 2 were Negroes. However, girls predominated in Regimen I and boys in Regimen II. The dosage groups differ with respect to race, white predominating in the low dose group and nonwhites in the high dose group. The range in the length of the interval between the first symptom and start of treatment was similar in the various dosage and regimen groups.

Details of the admission characteristics are shown on table 2.

RESULTS

Course of Illness.—Fatalities: Of the six patients who died, three developed advanced tuberculous meningitis with hydrocephalus and succumbed after 110, 125 and 130 days of treatment. The exact cause of death in two who died at two and nine days was not apparent but they had overwhelming infection on admission. The remaining fatality occurred at 21 days from extensive mediastinal emphysema which involved most of the subcutaneous tissues of the trunk, neck and head. This child had postmortem evidence of early tuberculous meningitis.

These results suggest that the outlook for recovery is good if the patient survives the first few weeks of treatment and if meningitis does not develop.

Survivors: Twenty-six patients were alive 12 months after the start of treatment although two were not doing well. One patient had developed tuberculous meningitis at 335 days of observation and the other had severe aspiration pneumonia. Two patients had other complications which responded to drug therapy: a tuberculous abcess of the foot and

TABLE 2

CHARACTERISTICS OF 32 MILIARY PATIENTS ON ADMISSION TO STUDY, BY TREATMENT REGIMEN AND INITIAL STREPTOMYCIN DOSE

Characteristic on admission to study	Total	No.				Per cent			
		Regimen		Initial streptomycin dose		Regimen		Initial streptomycin dose	
		I	II	Low*	High†	I	II	Low*	High†
All patients	32	18	14	10	22	100.0	100.0	100.0	100.0
Age (mo.)									
23 or less	23	13	10	5	18	72.2	71.5	50.0	81.8
24–59	6	3	3	4	2	16.7	21.4	40.0	9.1
60 or more	3	2	1	1	2	11.1	7.1	10.0	9.1
Race									
White	15	8	7	8	7	44.4	50.0	80.0	31.8
Nonwhite	17	10	7	2	15	55.6	50.0	20.0	68.2
Sex									
Male	17	7	10	5	12	38.9	71.4	50.0	54.5
Female	15	11	4	5	10	61.1	28.6	50.0	45.5
Other pulmonary involvement									
Active	30	18	12	9	21	100.0	85.8	90.0	95.5
Calcified	1	0	1	0	1	0.0	7.1	0.0	4.5
None	1	0	1	1	0	0.0	7.1	10.0	0.0
Temperature (rectal centigrade)									
37.5°–38.0°	8	3	5	3	5	16.7	35.7	30.0	22.7
38.1°–39.5°	18	13	5	4	14	72.2	35.7	40.0	63.7
39.6° and over	6	2	4	3	3	11.1	28.6	30.0	13.6
Days from first symptoms to treatment									
4 or less	1	1	0	0	1	5.6	0.0	0.0	4.5
5–15	7	4	3	2	5	22.2	21.4	20.0	22.7
16 or more	24	13	11	8	16	72.2	78.6	80.0	72.8

* Streptomycin 20 mg./kg. intramuscularly b.i.d. Some of these patients were subsequently retreated with higher dose.

† Streptomycin 50 mg./kg. intramuscularly b.i.d. to maximum of 1.5 gm. twice daily.

cervical adenitis. Pulmonary or extrapulmonary foci, which were found in all but one patient on admission, have not been considered complications since they preceded the acute dissemination and were probably an essential link in its pathogenesis.

The patients who did well under treatment showed a fairly consistent pattern of response. Most were noticeably improved and afebrile after 7 or 8 weeks and only 3 patients remained febrile longer than 14 weeks.

Miliary densities observed on chest RGs cleared more slowly. Although barely perceptible miliary opacities on the pretreatment RGs of one child had apparently cleared at 46 days, for only 12 children had densities cleared by 5 months after the start of treatment. Of 25 patients with adequate serial RGs, 24 were without roentgenographic evidence of miliary dissemination by one year of observation. The remaining child whose clinical course was good showed some but not complete roentgenographic clearing at 346 days. Disappearance of miliary lesions could not be determined in one boy wearing a body cast. At 167 days his film still retained some miliary shadows, but clinical improvement had been gratifyingly prompt. Miliary opacities visible on the film of one patient had cleared completely after 115 days despite the development of tuberculous meningitis. She died 10 days after her RGs had cleared.

Survival According to Regimen and Dosage Scheme: It is not possible with groups of this size to tell whether the differences shown in table 3 in the survival status of the

TABLE 3

SURVIVAL STATUS OF MILIARY PATIENTS AT ONE YEAR, BY REGIMEN AND INITIAL STREPTOMYCIN DOSE

Status at 1 yr.	Total	Regimen		Initial streptomycin dose	
		I	II	Low*	High†
All patients	32	18	14	10	22
Living and well	24	15	9	5	19
Living and not well	2	1	1	1	1
Dead	6	2	4	4	2

* Streptomycin 20 mg./kg. intramuscularly b.i.d. Some of these patients were subsequently retreated with higher dose.

† Streptomycin 50 mg./kg. intramuscularly b.i.d. to maximum of 1.5 gm. twice daily.

regimen groups at 12 months are the result of treatment or of chance variation. A larger clinical experience is necessary before definitive conclusions can be drawn as to whether the addition of promizole® actually results in a higher proportion of cases on Regimen I living at one year.

Differences of a greater magnitude are apparent when the patients are grouped according to whether they were initially treated with the "low" dose of streptomycin. While the number of children in each group is small, the contrasts in survivorship are great enough to suggest that the 20 mg./kg. dose twice a day was inadequate, and that 50 mg./kg. twice a day may be closer to the optimum dose.

Prognostic Value of Clinical and Laboratory Data on Admission: Other workers have attempted to correlate the condition of the patient at the start of treatment with his eventual response under treatment. Table 4 shows the results of such a tabulation for the patients in this study. These children apparently fared about the same regardless of age, race or sex.

The duration of illness before the start of treatment may have been of some importance. Only 1 of 8 patients treated within 15 days of the onset of symptoms died, whereas 5 of the 24 patients in whom there was a delay of 16 or more days succumbed. These differences are not striking, but they do confirm the findings of others.

Duration of Treatment During the First Year: The average duration of streptomycin

TABLE 4

CHARACTERISTICS OF 32 MILIARY PATIENTS ON ADMISSION TO STUDY, BY SURVIVAL AT 12 MONTHS

Characteristic on admission to study	No.			Per cent		
	Total	Living	Dead	Total	Living	Dead
All patients	32	26	6	100.0	81.3	18.7
Age (mo.)						
23 or less	23*	19*	4	100.0	82.6	17.4
24–59	6	4	2	100.0	66.7	33.3
60 or more	3	3	0	100.0	100.0	0.0
Race						
White	15	12	3	100.0	80.0	20.0
Nonwhite	17	14	3	100.0	82.4	17.6
Sex						
Male	17	14	3	100.0	82.4	17.6
Female	15	12	3	100.0	80.0	20.0
Temperature (rectal centigrade)						
37.5°–38.0°	8	7	1	100.0	87.5	12.5
38.1°–39.5°	18	16	2	100.0	88.9	11.1
39.6° and over	6	3	3	100.0	50.0	50.0
Days from first symptoms to treatment						
4 or less	1	1	0	100.0	100.0	0.0
5–15	7	6	1	100.0	85.7	14.3
16 or more	24	19	5	100.0	79.2	20.8

* One patient is living but has meningitis.

treatment among the patients who survived was 138 days, with a range of 42 to 286 days (one to seven 6 week courses), Para-aminosalicylic acid and promizole® were continued 4½ months beyond streptomycin. Three of the patients reported well at one year had received only one course of streptomycin and two were treated with the low dose. Seven received only two courses. For those who did not survive, death itself in most cases terminated treatment.

Drug Toxicity: The manifestations reported to the central office may not constitute a full account of the toxicity occurring in this series. Those described here are grouped according to their probable cause, based on the toxic effects characteristic of the drugs used and the time relationship between the administration of the drug and the appearance of the symptom.

Because testing for vestibular damage was optional, it was not possible to determine the frequency with which it occurred. A notation of normal vestibular function, unsupported by caloric or rotation tests, was not accepted as conclusive. Complete loss of caloric response was noted in about half the patients who were tested often enough to make this observation of value.

Vomiting occurred with almost equal frequency in patients on the two regimens and was rarely severe enough to interfere with nutrition. For two children oral medication had to be stopped for 7 to 10 days, but was successfully reinstituted.

Some workers have found thyroid enlargement may be associated with promizole® therapy. In this study, 4 patients on Regimen I, which includes promizole®, developed palpably enlarged thyroid glands but showed no endocrine imbalance. The enlargement was diffuse, never great enough to cause mechanical difficulties, and in 3 of the 4 disappeared before promizole® was discontinued. One child treated without promizole® developed a palpable thyroid gland with enlargement estimated at 50% after 6 months of observation. After 12 months the gland was considered palpable but not enlarged. No physical evidence of hormone changes was noted.

Local nodule formation around the site of intramuscular streptomycin injection regressed at the end of treatment, and did not contraindicate further streptomycin.

Transient red discoloration of the urine, usually in the second week of promizole® treatment, was apparently due to the excretion of a detoxification product of promizole®. It was not accompanied by hematuria, hemoglobinuria or porphyrinuria. No patient showed evidence of self-hemoglobinemia or methemoglobinemia.

Moderate anemia was often seen. With one exception this disappeared as the patients improved even though medication was discontinued.

Streptomycin Resistance: All but one of the patients who had positive cultures on admission harbored tubercle bacilli initially sensitive to streptomycin. The extensive chemotherapy and generally good response to treatment made it impossible to obtain an adequate series of cultures for study of development of bacterial resistance.

The patient who had a streptomycin-resistant strain at admission had probably been infected by her father. He was at home with open pulmonary tuberculosis and had received streptomycin. This girl developed meningitis and died after 125 days of observation.

Discussion and Summary

Two combinations of drugs were compared in a cooperative study of 32 children with acute hematogenous miliary tuberculosis treated at seven different pediatric centers under a common protocol. Eighteen children were given intramuscular streptomycin with oral para-aminosalicylic acid and promizole®; 14 children were given streptomycin and para-aminosalicylic acid without promizole®. A one year follow-up of this small group showed no significant differences in the results due to the use of promizole®. However, 5 of 10 children treated initially with a streptomycin dose of 20 mg./kg. intramuscularly twice a day were either dead or had developed meningitis, while only 2 of 22 children treated with a 50 mg. dose died, one of these having developed meningitis.

Twenty-six of the original 32 patients were alive 12 months after the start of treatment. Relapse of miliary disease was not encountered during the first year of this study.

The optimum duration of treatment is still uncertain. The combination of para-aminosalicylic acid with streptomycin may be assumed to delay the emergence of streptomycin-resistant organisms in miliary and meningeal diseases just as it does in pulmonary tuberculosis. Thus, a six month or even one year course of streptomycin can now be considered feasible. Although some patients may have been treated longer than necessary, the observation that three patients developed meningitis at 110, 125 and 130 days of study suggests that treatment should be relatively long. A child who survives miliary tuberculosis only to develop tuberculous meningitis has received little real benefit from therapy. As the over-all mortality in miliary tuberculosis is lowered, the prevention of meningitis in the survivors becomes an increasingly important goal.

Disturbing side effects of promizole® therapy were less frequent among the patients

reported here than among other reported groups. The daily dose, however, was small in comparison with the amounts recommended by Lincoln.

Addendum*

Follow-up reports for the 26 survivors were submitted by the original investigator on or after April 1, 1952. This represented a span of 2 to 4 years from the first day of treatment, depending on date of admission to study. All 26 patients were still alive.

Twenty of the 24 children who had been in good condition without gross handicap or residua at the end of one year remained well. None of these developed sequlae or relapsed, and none received further treatment. Three children, in all of whom the miliary lesions had cleared, were suffering from other types of tuberculosis in April 1952 (34 to 40 months after admission to study). One boy whose tuberculosis of the spine was recognized at admission was still in the hospital but was not receiving chemotherapy. Another still had active pulmonary tuberculosis. A girl was under observation for suspected renal tuberculosis. Finally, a boy who had been well at one year of study developed meningitis at 417 days. He was subsequently treated and recovered by April 1952 (43 months) except for a speech defect occasioned by deafness.

Follow-up beyond 12 months revealed appreciable improvement for the two children who had been in poor condition. The boy whose miliary disease had been complicated by meningitis at 335 days of study was home, without residua, and no longer required drug therapy. The girl whose miliary course had been complicated by aspiration pneumonia was completely well by April 1952.

It can then be said that 2 to 4 years after initiation of treatment in a series of 32 infants and children with miliary tuberculosis, 26 were living without evidence of miliary disease.

II. Tuberculous Meningitis

Diagnostic Criteria.—Conclusive proof of the diagnosis by cerebrospinal fluid culture, autopsy or biopsy was obtained in 77 patients, who had, in addition, clinical and spinal fluid changes in accord with a diagnosis of tuberculosis of the meninges.

Sixteen patients with neither positive cerebrospinal fluid nor autopsy verification are included because for each case clinical and laboratory data pointed to a diagnosis of tuberculous meningitis and to no other. The 16 children with a "probable" diagnosis had the following findings in common: a positive tuberculin reaction, characteristic clinical signs and symptoms of meningitis, abnormalities of the cerebrospinal fluid characteristic of tuberculous meningitis, cerebrospinal fluid smears and cultures negative for other pathogens, and roentgenographic evidence of pulmonary or extrapulmonary tuberculosis.

Characteristics on Admission.—In table 5 are shown the characteristics of all patients at the start of treatment. The 93 patients are grouped by regimen, and also by the initial dose of intramuscular streptomycin.

Representative of the usual frequency of the disease in childhood, more than half the patients were less than 2 years of age. The oldest child was 14 years and 9 months when admitted to the study.

The stage of the disease was estimated on admission according to the criteria used by the British Medical Research Council:[2]

Early: Patients with mainly nonspecific symptoms, little or no clinical signs of meningi-

* Since the detailed report of the 12 month course of these patients was prepared, it has been possible to obtain further information included in this Addendum.

TABLE 5

CHARACTERISTICS OF 93 MENINGEAL PATIENTS ON ADMISSION TO STUDY, BY TREATMENT REGIMEN AND INITIAL STREPTOMYCIN DOSE

Characteristic on admission to study	Total	No.				Per cent			
		Regimen		Initial streptomycin dose		Regimen		Initial streptomycin dose	
		I	II	Low*	High†	I	II	Low*	High†
All patients	93	46	47	24	69	100.0	100.0	100.0	100.0
Age (mo.)									
23 or less	47	22	25	16	31	47.8	53.2	66.7	44.9
24–59	26	14	12	5	21	30.4	25.5	20.8	30.5
60 or more	20	10	10	3	17	21.7	21.3	12.5	24.6
Race									
White	66	31	35	18	48	67.4	74.5	75.0	69.6
Nonwhite	27	15	12	6	21	32.6	25.5	25.0	30.4
Sex									
Male	48	24	24	13	35	52.2	51.1	54.2	50.7
Female	45	22	23	11	34	47.8	48.9	45.8	49.3
Type of illness									
Meningeal alone	70	35	35	16	54	76.1	74.5	66.7	78.3
Meningeal and miliary	23	11	12	8	15	23.9	25.5	33.3	21.7
Tuberculous foci									
Active pulmonary (including miliary)	69	33	36	22	47	71.7	76.6	91.8	68.1
Extrapulmonary only	7	3	4	1	6	6.5	8.5	4.1	8.7
Calcified pulmonary only	8	4	4	0	8	8.7	8.5	0.0	11.6
None apparent	9	6	3	1	8	13.0	6.4	4.1	11.6
Stage									
Early	15	8	7	3	12	17.4	14.9	12.5	17.4
Intermediate	24	9	15	7	17	19.6	31.9	29.2	24.6
Advanced	54	29	25	14	40	63.0	53.2	58.3	58.0
Mental state									
Alert	29	15	14	6	23	32.6	29.8	25.0	33.3
Not alert	64	31	33	18	46	67.4	70.2	75.0	66.7
Temperature (rectal centigrade)									
37.5°–38.0°	20	10	10	7	13	21.7	21.3	29.2	18.8
38.1°–39.5°	62	32	30	15	47	69.6	63.8	62.5	68.1
39.6° and over	11	4	7	2	9	8.7	14.9	8.3	13.1
Days from first symptoms to treatment									
4 or less	14	7	7	5	9	15.2	14.9	20.8	13.1
5–15	46	21	25	13	33	45.6	53.2	54.2	47.8
16–25	19	9	10	4	15	19.6	21.3	16.7	21.7
26 or more	14	9	5	2	12	19.6	10.6	8.3	17.4

* Streptomycin 20 mg./kg. intramuscularly b.i.d. Some of these patients were subsequently retreated with higher dose.

† Streptomycin 50 mg./kg. intramuscularly b.i.d. to maximum of 1.5 gm. twice daily.

tis, no paresis, in good general condition and fully conscious. Diagnosis established mainly on findings in cerebrospinal fluid.

Advanced: Patients obviously extremely ill, deeply stuporous or comatose, or with gross paresis.

Intermediate: Patients in a condition between those of the first two groups.

Only 14 patients were treated as early as the fourth day of symptoms. This delay is a reflection of the difficulty of recognizing meningitis, not on the mechanics of the study which provided for treatment within 24 hours of admission.

The cerebrospinal fluid studies prior to the start of treatment are not reported here because in almost every instance the deviations from normal were characteristic. Pleocytosis was usually below 250 cells/cmm. and lymphocytes predominated. Chlorides were almost invariably low. For the most part, protein levels ranged between 40 and 160 mg./100 cc. The least common abnormality, a low sugar (40 mg./100 cc. or less) was found in only 78 patients.

Initial Comparability of Regimen and Dosage Groups.—The composition of Regimens I and II is similar and it appears that important variables affecting the course of the disease were effectively controlled by the random allocation of patients between regimens. The two dosage groups unlike the regimen groups were not the product of randomization but the result of a change in the dosage schedule during the study. The low and high dose groups are dissimilar with respect to tuberculous foci and age. More of the low dose group had active pulmonary foci than the high dose group. The low dose group included more infants.

Results

Course of Illness.—Fatalities: At the end of 12 months of study 51 patients were dead. For most of these children the course was one of rapid deterioration. Over half the deaths (27) occurred in the first six weeks; almost all (47) had occurred by six months of study.

The prevalence of early fatality may be illustrated by application of the life table technic. A theoretic cohort of 1,000 meningeal patients, all beginning treatment on the

TABLE 6

Number of Meningeal Patients Out of Cohort of 1,000 Surviving to Indicated Point of Time

(based on 1 yr. of observation for 93 patients)

Length of survival (days)	No. of patients surviving
0	1,000.00
30	744.44
60	678.64
90	615.86
120	540.68
150	508.68
180	487.27
210	487.27
240	476.67
270	465.83
300	455.24
330	444.44
360	444.44

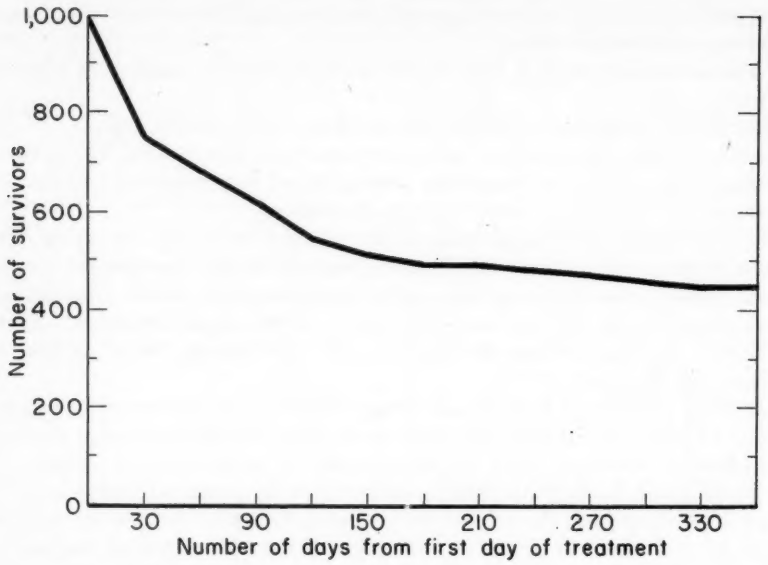

CHART 1. Survivorship curve based on 93 meningeal patients surviving to indicated point of time.

same day, are assumed to have suffered the same mortality experience as that which was actually encountered by the 93 children treated. The tabulations of survivorship appear in table 6. The material is presented graphically in chart 1, in which the horizontal axis represents number of days beginning with the first day of treatment, the vertical axis the number of patients surviving. Both the chart and the table show the tremendously large number of deaths during the first month of treatment.

No child who succumbed during the first year ever showed normal cerebrospinal fluid and physical findings in the period of study. Thirty-six patients had an uninterrupted downhill course and died between the first and 150th day. On the other hand, 15 patients either remained unchanged for at least six weeks or showed slight improvement before death. They survived 66 to 304 days.

Deaths which occurred early usually were associated with markedly increased intracranial pressure and respiratory failure. All autopsy examinations, including those for children treated only a few days, revealed some degree of hydrocephalus.

Two children died of intercurrent disease. Staphylococcic septicemia with secondary meningitis was responsible for death in a child whose streptomycin therapy had ended two months previously. Another child died of hemorrhage from a peptic ulcer which had penetrated to the pancreaticoduodenal artery. Although the peptic ulcer may have been secondary to the central nervous system disease, hemorrhage was the primary cause of death.

Deaths occurring after the first 2 or 3 months of treatment were commonly preceded by a stage of irreversible spasticity and coma often associated with advanced marasmus. Pathologic findings of marked hydrocephalus, thrombosis and endarteritis of the cerebral vessels, and organization of exudate about the brain stem and optic chiasm were noted.

Survivors: Forty-two patients survived the first year. Twenty-four, of whom 20 had shown steady improvement and 4 had improved after relapse, were in remarkably good

condition. They were active, alert, and had normal or near normal intelligence. The cerebrospinal fluid was essentially normal and neurologic abnormalities were minimal.

The abnormalities in the cerebrospinal fluid which improved first were the sugar and chloride levels which often reached normal after only six weeks of treatment. Protein content and cells responded more slowly and, with successful treatment, usually showed a somewhat erratic downward trend over a period of months. A marked increase in cells was sometimes seen for a day or two during late convalescence, but this was not associated with exacerbation of meningitis.

The remaining 18 survivors failed to show significant improvement and had severe sequelae including gross neurologic abnormalities, mental retardation and hydrocephalus. Most still had abnormal findings in their cerebrospinal fluid. Six still had persistently active meningitis. Two of these six, along with 14 other children, had extensive and irreversible brain damage. Though their lives were prolonged by treatment, it is hard not to consider them therapeutic failures.

The course of illness among the 18 children who were in poor condition at the end of one year was not uniform. Eight of the patients had made continuous but insignificant gains; 6 had deteriorated before slight progress set in; and 4 had experienced a relapse from which recovery was negligible.

Relapse: For the purpose of this study, relapse is defined as the reappearance of meningitis in a patient who had normal cerebrospinal fluid and had been apparently free of meningitis for at least 30 days. In all, 8 patients experienced a relapse of meningitis during the first year. Five of the 8 were initially treated with the low dose. The shortest period of time from cessation of streptomycin therapy to relapse was 50 days and the longest was 247 days. A drop in the sugar content of the cerebrospinal fluid after a period of normality almost always heralded a relapse.

All patients who showed relapse were subsequently re-treated with streptomycin, and all were living at 12 months, although two still had positive cultures from cerebrospinal fluid and two others finished the year in poor condition.

Survival According to Regimen and Dosage Scheme: Table 7 shows the survival status at 12 months of all patients according to treatment regimen and according to initial dose of intramuscular streptomycin. The almost identical outcome with Regimens I and II is striking. Despite the limitations of analysis based upon so small a sample, the number of survivors under the high dose program and their superior condition appear to sub-

TABLE 7

SURVIVAL STATUS OF MENINGEAL PATIENTS AT ONE YEAR, BY REGIMEN AND INITIAL STREPTOMYCIN DOSE

Status at 1 yr.	Total	Regimen		Initial streptomycin dose	
		I	II	Low*	High†
All patients	93	46	47	24	69
Living and well	24	12	12	2	22
Living and not well	18	9	9	5	13
Dead	51	25	26	17	34

* Streptomycin 20 mg./kg. intramuscularly b.i.d. Some of these patients were subsequently retreated with higher dose.

† Streptomycin 50 mg./kg. intramuscularly b.i.d. to maximum of 1.5 gm. twice daily.

TABLE 8

CHARACTERISTICS OF 93 MENINGEAL PATIENTS ON ADMISSION TO STUDY, BY SURVIVAL AT 12 MONTHS

Charac'eristic on admission to study	No.			Per cent		
	Total	Living	Dead	Total	Living	Dead
All patients	93	42	51	100.0	45.2	54.8
Age mo.)						
23 or less	47	15	32	100.0	31.9	68.1
24-59	26	12	14	100.0	46.2	53.8
60 or more	20	15	5	100.0	75.0	25.0
Race						
White	66	32	34	100.0	48.5	51.5
Nonwhite	27	10	17	100.0	37.0	63.0
Sex						
Male	48	24	24	100.0	50.0	50.0
Female	45	18	27	100.0	40.0	60.0
Type of illness						
Meningeal alone	70	35	35	100.0	50.0	50.0
Meningeal and miliary	23	7	16	100.0	30.4	69.6
Tuberculous foci						
Active pulmonary (including miliary)	69	27	42	100.0	39.1	60.9
Extrapulmonary only	7	3	4	100.0	42.9	57.1
Calcified pulmonary only	8	6	2	100.0	75.0	25.0
None apparent	9	6	3	100.0	66.7	33.3
Stage						
Early	15	8	7	100.0	53.3	46.7
Intermediate	24	12	12	100.0	50.0	50.0
Advanced	54	22	32	100.0	40.7	59.3
Mental state						
Alert	29	15	14	100.0	51.7	48.3
Not alert	64	27	37	100.0	42.2	57.8
Temperature (rectal centigrade)						
37.5°–38.0°	20	7	13	100.0	35.0	65.0
38.1°–39.5°	62	30	32	100.0	48.4	51.6
39.6° and over	11	5	6	100.0	45.5	54.5
Days from first symptoms to treatment						
4 or less	14	6	8	100.0	42.9	57.1
5–15	46	21	25	100.0	45.7	54.3
16–25	19	10	9	100.0	52.6	47.4
26 or more	14	5	9	100.0	35.7	64.3

stantiate the superiority of that program.

Prognostic Value of Clinical and Laboratory Data on Admission: In table 8 various characteristics of the patients on admission are related to survivorship at the end of 12 months of study.

The coexistence of miliary tuberculosis has been reported to influence unfavorably the prognosis in tuberculous meningitis. The differences reflected in table 8 are in this direction. In no instance did previously unsuspected miliary tuberculosis become clinically evident once treatment for meningitis had been started. In 3 children, all of whom died within 11 days after the start of treatment, there was evidence of early miliary dissemination at autopsy although clinical evidence had been lacking during life.

The presence of active pulmonary tuberculosis also appears to worsen the prognosis, although the data in table 8 are probably misleading when considered out of context. Infants, who have the poorest prognosis, almost always have active pulmonary tuberculosis when their meningitis is first discovered. The evidence suggests that age, rather than the activity of the pulmonary disease, is responsible. The average age of 24 patients without an active pulmonary focus was 5½ years, in contrast to 2½ years for the other 69.

Older children fared far better than infants. The survival rate was somewhat higher among boys than girls and higher among white than nonwhite children. These findings are similar to the experience of others.

Duration of Treatment During the First Year in the Survivors: During the first year of study, the 42 survivors received, on the average, streptomycin for 179 days; 180 days on Regimen I and 178 on Regimen II. There was, however, considerable variation among patients, ranging from 1 to 7 courses of streptomycin, usually 4 or 5. In one case, streptomycin was discontinued after 35 days because of an apparently hopeless condition. Paradoxically, this child's cerebrospinal fluid was normal by six months with no therapy other than para-aminosalicylic acid and promizole®, and at one year he was still alive although he had extensive brain damage.

Since para-aminosalicylic acid and promizole® were continued 4½ months after the completion of the last course of streptomycin, the average patient was given continuous therapy with one or both of these drugs during the first year and streptomycin for about half that time.

The 10 Day Rest Period: The rest period after each course of streptomycin was specified by the common protocol as a research tool. Theoretic considerations originally suggested that periodic interruption of streptomycin therapy might delay the emergence of streptomycin-resistant bacilli, facilitate subsequent bacteriologic studies, reduce signs of meningeal irritation and permit more accurate evaluation of the cerebrospinal fluid. However, results in this respect are inconclusive.

Supplementary Treatment: While any form of treatment other than the administration of additional tuberculostatic drugs was permitted, the only other important therapy used was designed to improve the flow of cerebrospinal fluid. Such measures and their results are briefly described below.

Surgical procedures for lysis of adhesions or for ventricular decompression performed in eight patients sometimes allowed direct instillation of streptomycin into the ventricular system.

With material furnished by Dr. William Tillett and in accordance with his procedures,[3] streptokinase-streptodornase solutions were given intrathecally to five patients in an effort to relieve spinal block or lyse exudate at the base of the brain. The results were inconclusive.

With similar intent a specially prepared solution of purified protein derivative (Seibert) was administered intrathecally for two patients according to the recommendations of Cairns et al.[4] and Smith and Vollum.[5] Both had developed decerebrate rigidity

and both eventually died. Autopsy performed in one of these patients showed a brain stem remarkably free of exudate.

Drug Toxicity: When 2 or 3 drugs, all known to have some toxic properties, are given concurrently to patients suffering from a disease which may have capricious systemic and local manifestations, it is difficult to name the responsible drug. This is peculiarly true in a study of tuberculous meningitis because survival has been observed only with streptomycin therapy. Prior to the use of this drug, there was no opportunity to study the residual effects of the disease process. Within these limitations, manifestations reported are grouped according to their probable cause.

Unquestionably the most common toxic reaction to large doses of parenteral streptomycin is the loss of vestibular function. A significant number of meningeal patients treated with 50 mg./kg. twice daily for more than six weeks had definite vestibular dysfunction. However, children with minimal cerebral damage were able to compensate for the defect over a period of months.

Deafness was observed in 8 of the 42 survivors. Three of the patients with hearing loss were 11, 18 and 45 months of age at the start of treatment. They suffered extensive brain damage and had abnormalities of other cranial nerves. Their deafness was probably the result of the disease. The remaining five patients were older children who received large amounts of streptomycin for 160 or more days. They were in relatively good condition at the end of 12 months. Despite absence of other central nervous system damage, it is unrealistic to implicate intramuscular streptomycin as the sole cause of deafness in these patients. Intrathecal administration of streptomycin or the meningitis itself could have been responsible. The same intramuscular dose did not produce hearing difficulty in a single miliary patient.

Reactions to intrathecal streptomycin, chiefly acute episodes after an injection, became less frequent after the first few weeks of treatment. Vomiting was usually accompanied by twitching, dizziness or headache. Febrile reactions frequently followed intrathecal injections, but only one patient reacted so violently that intrathecal therapy was discontinued.

Two patients had generalized convulsions shortly after a single injection. Another child developed minor convulsive episodes toward the end of each six week course, which ceased temporarily during the rest periods and disappeared permanently when intrathecal treatment was discontinued. One patient developed coma and shock after the first intrathecal injection and died the following day. Another patient went into a shocklike state for about an hour after each of her first 10 injections, but subsequently tolerated them well. Shock and stupor accompanied by paralysis of the lower extremities lasted about six hours after an injection in a third patient, who recovered completely and did not react to subsequent injections.

The only side effect attributable to para-aminosalicylic acid was vomiting, almost universal with the first few doses, but less frequent later in the course of treatment. In five patients vomiting was so severe that medication was stopped.

Transient red discoloration of the urine was noted among patients who received promizole® but was universally benign. Nontoxic diffuse goitre during promizole® treatment was seen in only one patient, who also had slight precocious enlargement of the nipples and slight hirsutism. These changes disappeared by the end of the first year. A syndrome of cyanosis associated with methemoglobinemia, elevation of blood nonprotein nitrogen and albuminuria developed in one patient after 4½ months of promizole®. The abnormalities disappeared when the drug was withdrawn for a week, and reappeared

promptly when the drug was reinstituted. Promizole® was therefore permanently discontinued.

Streptomycin Resistance: Adequate information of the development of streptomycin resistance is not available because a series of positive cultures was obtained from very few patients.

Two children, previously untreated with streptomycin, were found to have organisms resistant to at least streptomycin 100 μg./cc. on admission to the study. Each had been exposed at home to an adult who had undergone streptomycin treatment. Both children died.

Discussion and Summary*

Ninety-three children with tuberculous meningitis, 23 of whom also had miliary tuberculosis, were observed for a period of one year while under treatment with a combination of tuberculostatic agents. Half the patients were given intramuscular streptomycin, intrathecal streptomycin, and para-aminosalicylic acid and promizole® by mouth. The remainder received an identical regimen except that promizole® was omitted.

Forty-two patients (45%) survived the first year; 24 of these had no serious sequelae from the disease. No differences were noted in the course of the disease among those who received promizole® and those who did not, and the one year survival rates in the two groups were practically identical.

Revision of the streptomycin dosage, which took place after the study had been in progress seven months, produced results which appear to justify the change. An intramuscular streptomycin dose of 50 mg./kg. twice daily to a maximum of 1.5 gm. twice daily was apparently more effective than 20 mg./kg. twice daily.

Lincoln[6] whose results in childhood meningitis are the most successful yet reported and the British Medical Research Council[2] both depend on a regimen which includes intrathecal streptomycin. The investigators in this study favor its use and had no unusual difficulty with it.

Relapse occurred in eight children, all of whom survived the first year.

A poorer prognosis was noted in infants, in nonwhites, and in patients with miliary tuberculosis.

The most common toxic effects were due to streptomycin, which caused vestibular damage in a large number of patients, but the capacity of children to compensate for this dysfunction is so great that this risk is minor in the face of the otherwise hopeless outcome. Streptomycin may have been partially responsible for marked hearing loss in six.

Para-aminosalicylic acid and promizole® act less rapidly than streptomycin. They are easily administered and rarely produce significant toxicity even when given over extended periods. They appear to reinforce the effect of streptomycin, and para-aminosalicylic acid at least postpones the emergence of streptomycin resistance. Their use appears to decrease the likelihood of relapse. Finally, their daily use at home maintains the patient's awareness that he requires prolonged medical supervision and brings him back for examination when his drug supply needs replenishing. The use of these drugs with streptomycin in tuberculous meningitis is recommended.

Addendum*

The status of the 42 meningeal survivors was reviewed by the investigators in April,

* The reader is referred to p. 44 for the summary of miliary patients.

* Since the detailed report of the 12 month course of these patients was prepared it has been possible to obtain further information included in this Addendum and in the Addendum on miliary patients on p. 45.

1952, representing a span of 2 to 4 years from initiation of chemotherapy. One child had moved and could not be located. Three additional deaths and one late relapse were reported. Of these 4 patients, 2 had been treated with three drugs including promizole®, the other 2 had received only streptomycin and para-aminosalicylic acid. The three deaths occurred after 565, 623 and 759 days of study. All three children had been in poor condition at 12 months.

One girl whose condition was poor during the first year of observation subsequently improved only to relapse 46 months after the start of treatment, the only instance of relapse after a year of treatment.

Eleven of the children who had been in poor condition at 12 months continued to have gross residua although minor improvement was noted for several.

Three patients previously with gross handicaps improved markedly after 12 months. One boy, 4 years old at admission, had been difficult to arouse because of deafness. By April 1952 (32 months), he showed remarkable improvement according to psychometric test results. A one year old boy considered mentally retarded at 12 months of study was almost normal at 30 months follow-up. A third boy who had relapsed at 240 days was in excellent condition and completely without residua in April 1952 (43 months).

Of the 24 children who had been in good condition at completion of one year, one was lost from observation and the remaining 23 had no meningeal disease. However, one boy who at admission to study had no demonstrable pulmonary or other tuberculous focus developed osseous tuberculosis nearly three years later. Another child had not recovered from a lesion of the spine which had been recognized at admission 35 months earlier. Both children were still receiving chemotherapy. The remainder continued to do well, and three showed marked improvement over the 12 month status.

In summary, a series of 93 infants and children were treated for tuberculous meningitis. Two to four years after initiation of treatment 54 had died, 12 were living with gross residua, one patient could not be traced, and 26 were alive without significant sequelae from meningitis.

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SPANISH ABSTRACT

Quimioterapia de la Tuberculosis Miliar y de la Meningitis Tuberculosa

El empleo de la estreptomicina en el tratamiento de la tuberculosis miliar y de la meningitis tuberculosa ha demostrado que estos padecimientos no son fatales de necesidad; sin embargo, a pesar de este hecho algunos problemas quedan sin resolverse y otros han aparecido; por ejemplo, la efectividad de la estreptomicina en la tuberculosis miliar no impedía la aparición de la meningitis en algunos pacientes; la meningitis tuberculosa seguía presentando mortalidad muy alta y con frecuencia secuelas invalidantes; las recaídas meses después de la aparente curación persistían, etc.

Por estas y otras razones el Departamento de Salubridad de los Estados Unidos inició en 1948 un estudio con el uso combinado del promizol y /o ácido paraminosalicílico y estreptomicina como tratamiento de la tuberculosis meníngea y miliar.

Este plan incluyó dos regímenes terapéuticos: combinación estreptomicina-ácido paraminosalicílico (régimen No. 2) y esta combinación más promizol en un determinado número de pacientes (régimen No. 1); la estreptomicina se empleó por vía intratecal sólo en pacientes meníngeos.

La estreptomicina se aplicó en perídos de seis semanas, tantas veces como el estado del paciente lo indicara, estableciéndose un intervalo de descanso de diez días entre los períodos; tanto el ácido paraminosalicílico como el promizol se continuaron cuatro meses y medio después de completar la aplicación de la estreptomicina. Durante los primeros siete meses del estudio la dosis intramuscular de la estreptomicina fué de 20 miligramos por kilo de peso cada 12 horas, y dos miligramos por kilo de peso diariamente por cuatro días, y luego en días alternados, por la vía intratecal. En noviembre de 1948 se elevaron las dosis de estreptomicina intramuscular a 50 miligramos por kilo de peso cada doce horas y a 50 miligramos por dosis por vía intratecal, independientemente del peso del enfermo. El promizol se aumentó de 0.5 miligramos al día a la dosis necesaria para mantener un nivel sanguíneo de dos a tres miligramos por ciento, y posteriormente según su tolerancia, a un máximo de un gramo diario para niños menores de seis meses de edad y dos gramos al día para niños mayores. Se mantuvo durante todo el estudio una dosis diaria de 20 centigramos por kilo de peso de ácido paraminosalicílico.

Con estos dos planes de tratamiento se trataron 32 niños con tuberculosis miliar aguda y 93 niños con meningitis tuberculosa, 23 de los cuales también presentaron tuberculosis miliar.

Los efectos tóxicos más frecuentes se debieron a la estreptomicina, que causó trastornos vestibulares en gran número de pacientes; este riesgo es mínimo si se compara al pronóstico fatal de no emplearse la droga. El ácido paraminosalicílico y el promizol actúan menos rápidamente que la estreptomicina y muy raramente presentan reacciones tóxicas aun cuando se usen por períodos prolongados; refuerzan la acción de la estreptomicina y disminuyen las recaídas; el ácido paraaminosalicílico retarda la aparición de la resistencia a la estreptomicina; por último su uso en el hogar mantiene al paciente en contacto con el médico.

1. Tuberculosis miliar: De los 32 niños estudiados, 18 recibieron estreptomicina, ácido paraminosalicílico y promizol, y 14 únicamente estreptomicina y ácido paraminosalicílico. Un año después no se habían observado diferencias significativas en los resultados de ambos planes de tratamiento; sin embargo, 5 de 10 niños tratados inicialmente con 20 miligramos de estreptomicina por kilo de peso cada 12 horas habían fallecido o presentaron meningitis, mientras que fallecieron dos de los 22 niños tratados con la dosis de 50 miligramos, uno de los cuales desarrollando meningitis.

En abril de 1952 los 26 pacientes aún vivían, 20 de los 24 niños con buenas condiciones generales continuaban perfectamente bien, tres presentaron otros tipos de tuberculosis y el cuarto desarrolló una meningitis de la que se recuperó con un tratamiento posterior, dejando sordera como única secuela.

Los dos niños restantes que habían estado en malas condiciones al iniciarse el tratamiento mejoraron satisfactoriamente.

En resumen, los autores concluyen que de dos a cuatro años después de iniciado el tratamiento a una serie de 32 lactantes y niños con tuberculosis miliar, 26 viven sin manifestaciones del padecimiento.

2. Meningitis Tuberculosa: Se trataron 93 niños, 23 de los cuales también presentaron tuberculosis miliar; la mitad recibió un tratamiento con la combinación de las tres drogas y el resto sólo estreptomicina con ácido paraminosalicílico. Al finalizar el primer año 42 pacientes (45%) sobrevivían y de ellos 24 no presentaban ninguna secuela grave del padecimiento.

No se observó diferencia en el curso de la enfermedad entre los dos regímenes terapéuticos empleados.

Los 42 casos sobrevivientes fueron nuevamente revisados en abril de 1952, al alcanzarse un lapso de dos a cuatro años después de la iniciación del tratamiento. Uno se perdió de vista, tres habían fallecido y otro había recaído; de estos últimos cuatro, dos habían sido tratados con las tres drogas y los otros dos sólo con dos; los tres niños fallecidos presentaron malas condiciones generales a los doce meses del tratamiento. Otros once niños en malas condiciones a los doce meses presentaron secuelas graves.

De los 24 niños en buenas condiciones al finalizar el primer año de observación, uno se perdió de vista y el resto continuaba sin manifestaciones meningíticas.

En resumen, los autores presentan una serie de 93 lactantes y niños tratados con estreptomicina, ácido paraminosalicílico y promizol, de dos a cuatro años después de iniciado el tratamiento; 54 han fallecido, 12 viven con secuelas muy serias, uno se ha perdido de vista y 26 viven sin secuelas significativas de la meningitis.

Department of Health, Education, and Welfare, Public Health Service

PEPTIC ULCER IN CHILDHOOD

By BERTRAM R. GIRDANY, M.D.
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DURING the past year 45 children with roentgen and clinical findings suggesting the diagnosis of peptic ulcer have been seen at Children's Hospital of Pittsburgh. This paper presents the experience with these children.

Gastric ulcer occurs occasionally in the neonatal period. Perforation of such lesion is the most common cause of pneumoperitoneum in this age group. In older infants and children gastric or duodenal ulcers may be present in association with extensive burns, severe infections and cerebral disease. Cole[1] and Hollander and Stark[2] reviewed the literature pertinent to these lesions.

Donovan and Santulli[3] in 1945 reviewed the experience at Babies Hospital in New York and reported 10 patients with duodenal ulcer proved at surgery or necropsy. They suggested that peptic ulcer in childhood occurred more frequently than reported. Their data indicate that the adolescent with ulcer often has the onset of disease during the first decade of his life. Proctor[4] in 1925 showed that in some adults with peptic ulcer symptoms began in childhood.

Alexander[5] reported that 30 children in a group of 254 he examined over a five year period showed roentgen signs of duodenal ulcer. He concluded that duodenal ulcer was common in pediatric practice and should be given more frequent clinical consideration. He did not believe that the same nervous and emotional factors that operated in adults were present in childhood. Gillespie and Bliss[6] and Gillespie and Dukes[7] reported six children with duodenal ulcer and six with duodenitis. Morgan[8] stressed the need for complete studies of the duodenal bulb following barium meal with pressure devices and multiple spot films in the evaluation of abdominal pain in childhood.

MATERIAL

This report includes observations on 45 children; the youngest was 14 mo. of age and the oldest 11 yr. of age. There was none between 2 and 3 yr. of age, and the remaining patients were grouped evenly between 3 and 11 yr. There were 25 girls and 20 boys.

Forty-one children complained of recurrent paraumbilical abdominal pain often referred to the right hypochondrium. Four vomited and did not have pain. Ten complained of pain and vomiting. Five presented the clinical story of "cyclic vomiting."

The story was similar to that in adults with peptic ulcer. Pain occurred most frequently during the night waking the child from sleep. Many patients complained of distress in the morning on arising.

Five children volunteered that milk relieved their pain. Often the child or his parent had noted no association between pain and food ingestion, but in some instances there was a story of pain relieved by eating. Occasionally distress was exaggerated for short periods after meals before relief was obtained. This led to the story of pain aggravated by, and following, meals.

Pain before meals and in the evening before going to bed was usual. The child often screamed

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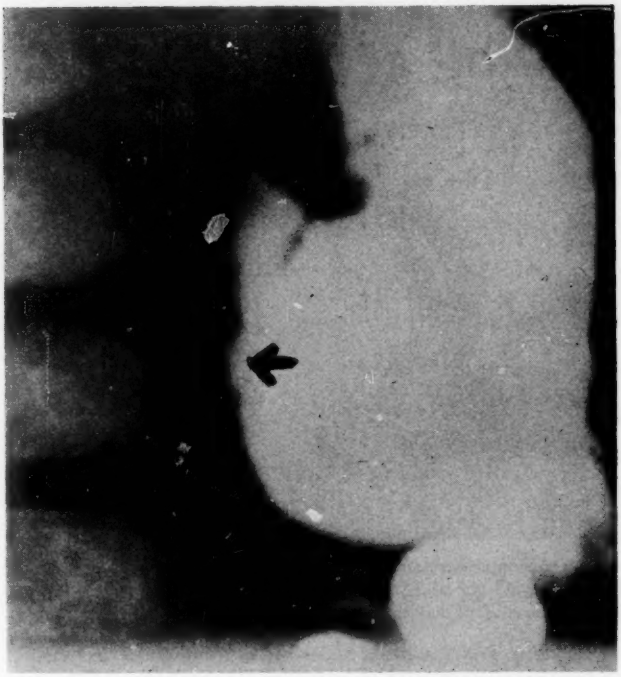

FIG. 1. Film made during GI series of 14 mo. old infant with complaint of vomiting of 3 wk.' duration. Small ulcer crater (see arrow) is seen along greater curvature. Ulcer crater was identified at surgery.

and "doubled-up" because of the intensity of his discomfort. In the younger patients it was not always clear whether the pain was real or the child was indicating the necessity to vomit. Some children experienced relief following vomiting.

During fluroscopic examination, the child frequently pointed directly to his duodenal bulb as the site of his pain, although he had previously given the story of pain referred to the hypogastric or paraumbilical region. Tenderness over the bulb on deep palpation was a uniform finding. Although the time of maximal distress was not volunteered, and the presenting complaint was abdominal pain "occurring all the time," direct questioning often elicited the characteristic story described.

Four of the children had no known history of pain with their vomiting. The youngest of this group was seen at 14 mo. of age with the complaint of vomiting of 3 wk.' duration. Following barium meal, an ulcer crater was demonstrated along the greater curvature of the stomach in the pre-pyloric region (Fig. 1). When medical treatment was not effective in relieving his vomitng, this child was explored surgically and gastroenterostomy done to by-pass the obstruction at the pylorus. Direct inspection showed a peptic ulcer in the pre-pyloric region of the stomach.

The duration of symptoms in the 45 children varied from 3 wk. to 5 yr. Individual attacks lasted minutes to hours.

There were 5 children with a history of cyclic vomiting. The episodes of vomiting began most frequently during the night, waking the child from sleep. Although vomiting was the only complaint, abdominal pain had been present in each case.

The roentgen criteria used in confirming the diagnosis of duodenal ulcer include the demonstration of ulcer crater and deformity of the duodenal bulb. Pylorospasm and localized tenderness to deep palpation over the bulb are helpful signs, but do not by themselves warrant a roentgen diagnosis of ulcer. Irritability of the duodenal cap is common in children and cannot be used as a diagnostic sign.

FIG. 2. Arrow is directed at ulcer crater in postbulbar portion of duodenum. Film of 8 yr. old girl with vomiting of 3 mo.' duration and weight loss of 13.6 kg. Postbulbar ulcer of duodenum was proved at surgery.

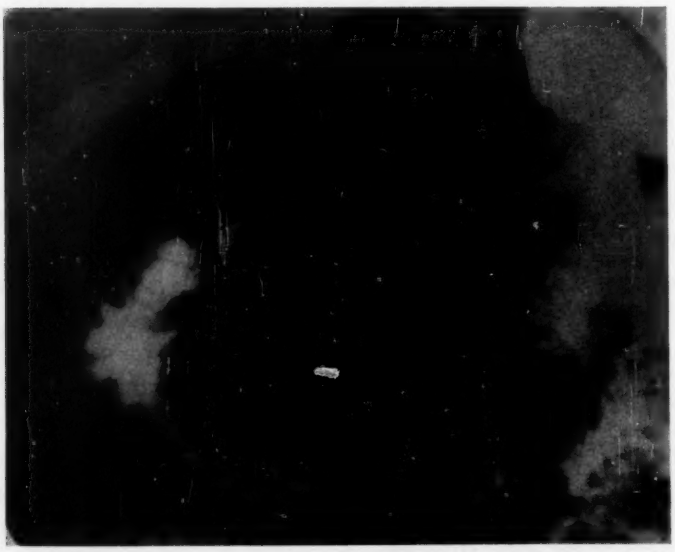

FIG. 3. Small ulcer crater with radiating folds is defined. Spot film of 5 yr. old girl with complaint of recurrent abdominal pain. At surgery for repair of umbilical hernia multiple adhesions about duodenum characteristically associated with ulcer were seen.

An 8 yr. old girl was admitted with the story of vomiting of 3 mo.' duration and weight loss of 13.6 kg. A diagnosis of postbulbar ulcer of the duodenum was made and medical regime instituted. The child improved in the hospital, but began to vomit again when she returned home. She was therefore explored surgically and gastroenterostomy carried out. At surgery a postbulbar ulcer in the duodenum at the site demonstrated on roentgen examination was identified (Fig. 2).

A 5 yr. old Negro girl was seen first with the complaint of recurrent abdominal paraumbilical pain preceding, and aggravated by, meals. A crater deformity (Fig. 3) was demonstrated in the duodenum following barium meal. She obtained complete relief of symptoms with dietary regime and aluminum hydroxide. Four months later elective surgical repair of an umbilical hernia was done. At surgery the duodenum was inspected directly, and multiple adhesions characteristically associated with ulcer were seen.

In these 2 children the diagnosis of ulcer was proved at surgery. The remaining patients in the group showed roentgen signs that were consistent with the diagnosis. They were similar clinically to those in whom the diagnosis was proved at surgery, and showed good response to medical therapy.

Results with Treatment

Treatment has consisted of diet with or without antacids or antispasmodics. Medication has not been used when dietary control alone has produced relief of symptoms. Marked improvement or complete subsidence of pain has been observed in all patients. The children with stories of cyclic vomiting have been asymptomatic to date for periods ranging from 3 to 12 months. In each instance such remission is longer than any previously observed before therapy was instituted.

Psychiatric investigations have not been conducted, but random observations have been made. With exceptions, the children included in this group are tense and bright and lack overt emotional lability.

The word "nervous" leaves much to be desired as a descriptive epithet, but it is interesting that it is a term commonly used by their parents to apply to this group of children. A characteristic comment is that "My child is so nervous I don't know what to do." Some parents have remarked that their children do not give ready expression to their feelings, and "keep things to themselves." The similarity to the adult ulcer patient "keeping the lid on" is strong.

Many of these children, during roentgen examination, were unusually quiet and reserved. While their colleagues might be expected to be noisy and uncooperative or raise objections, they were more apt to be cooperative and "suffer in silence." Under circumstances in which "nonulcer" children cried loudly, they were quietly tense, with tears welling up in their eyes. These observations cannot be documented as objective measures of nervous tension.

Five children had the onset of symptoms following abdominal trauma. One child was severely beaten by a group of her playmates while she was returning from school. Another was hurt while riding a sled in the snow. Two children were injured in automobile accidents. The relationship between head trauma and the postconcussion syndrome has been established; there may be parallel implications regarding abdominal trauma and peptic ulcer.

Two children first complained of pain after the arrival of a first sibling. Four others had pain at the beginning of school, and also showed morning vomiting. The teacher of one of these remarked that the child turned "white" with tense fear when he was addressed. One child's mother presented a characteristic obsessive compulsive neurosis regarding cleanliness.

A sensitive five year old Negro child, living in an area where fear and tension reach extremes, had her first episode of pain after one of the neighborhood children hanged

himself. Another child's episodes of cyclic vomiting began when she was 14 months of age after she had ingested the contents of a bottle of aspirin tablets.

Several children whose symptoms had been relieved by medical therapy had exacerbation of pain or vomiting during febrile illnesses. Recurrence of ulcer symptoms in association with stress is characteristic in adult patients. Two children have vomited blood during the course of measles infection.

Discussion

These observations do not form a closely related unit, but it is clear that emotional disturbances and psychic trauma are often present in children with signs and symptoms of peptic ulcer. The criteria used in diagnosis are a history of recurrent abdominal pain and/or vomiting over a prolonged period in a child who shows roentgen changes and makes satisfactory clinical recovery following therapeutic ulcer regime.

The roentgen diagnosis of ulcer is subject to the intrinsic limitations of the method. The author does not propose that all radiologists will accept the films of all his patients as diagnostic. Every set of films, however, has been reviewed by two or more experienced radiologists who have concurred in the interpretation of the film changes.

The diagnosis of ulcer may be questioned because the incidence reported here is greater than that generally recognized. Indeed these observations indicate that the disease is common. Should the teleologic diagnosis be open to question, there seems little doubt that these children do present a characteristic clinical syndrome which is worthy of attention.

There are implications that emotional and environmental factors are involved, and that they may be of major importance in explaining the incidence of peptic ulcer in these children. Preliminary observations support this view and suggest that ulcer in childhood is not necessarily different from the condition in adults. As noted earlier, many adult patients can trace their symptoms back to childhood.

The fact that five children with cyclic vomiting have shown signs of ulcer on roentgen examination, and have responded to therapeutic regimes raises the question, at least, of whether a large proportion of such children may have peptic ulcer as the underlying cause of their cyclic vomiting. More investigation is indicated.

Examination of gastric juice has not been done. It was felt that the information to be obtained did not justify the discomfort attendant on the procedure. Studies on blood pepsinogen are in progress and will be reported at a later date.

Summary

Peptic ulcer in childhood has been considered a relatively rare disease although sporadic reports of its occurrence have appeared. It has not usually been included in the differential diagnosis of conditions causing recurrent abdominal pain or vomiting in the pediatric patient. These data indicate that peptic ulcer is of frequent occurrence and constitutes an important pediatric problem. Psychogenic elements probably play an important role in the disease. The possible relationship of peptic ulcer to cyclic vomiting is suggested.

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SPANISH ABSTRACT

Ulcera Péptica en los Niños

Se presentan las observaciones de 45 niños con datos radiológicos y clínicos sugestivos del diagnóstico de úlcera péptica; el más pequeño tenía catorce meses de edad y el mayor once años; no hubo ningún caso entre los dos a tres años; el resto se agrupó de manera uniforme entre los tres y los once años de edad. La mayoría de los niños se quejaba de dolor abdominal paraumbilical recurrente, generalmente por la noche, antes de los alimentos o antes de acostarse. Cuatro de ellos al vomitar sentían alivio. Cinco niños presentaron el cuadro clínico de vómitos cíclicos. Radiológicamente se confirmaba el diagnóstico de úlcera péptica con el hallazgo de deformidad en el bulbo o bien de nicho ulceroso.

El tratamiento fue dietético, con o sin antiácidos o antiespasmódicos, no usándose éstos al obtenerse alivio de los síntomas con el control dietético. No se hizo en forma sistemática el estudio psíquico pero en los pocos casos observados, los niños eran del tipo inquieto, excitable e inestable emocionalmente. Se obtuvo la impresión general de que los trastornos emotivos y los traumas psíquicos se encuentran en el fondo de todo cuadro ulceroso.

Los autores concluyen que aun cuando es relativamente rara la frecuencia de la úlcera péptica, debe considerarse en el diagnóstico diferencial de los cuadros de dolor abdominal recurrente o vómitos cíclicos.

125 DeSoto Street

ADRENAL FUNCTION IN PREMATURE INFANTS

II. ACTH-Treated Infants and Infants Born of Toxemic Mothers

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THE newborn infant faces many handicaps in the neonatal period in meeting the suddenly imposed demands of an independent existence. Immaturity of some degree is manifest in most organs, and the endocrine glands share the immaturity. In particular the adrenal, with its overshadowing influence on physiologic processes, has an unusual developmental pattern[1] which has raised on morphologic grounds the question of adrenal insufficiency in the young infant. At birth the gland is large, but the zona glomerulosa is poorly differentiated, the zona fasciculata is very thin, the zona reticularis probably absent, and the medulla represented by a few scattered groups of cells. Eighty per cent of the gland is composed of the so-called fetal cortex, which is histologically distinct from the remainder of the gland and which abruptly degenerates in the first weeks of postnatal life. The influence of widespread necrosis in this zone on function is of obvious interest. A previous paper[2] outlines data obtained by the writer and by several other investigators on steroid excretion and electrolyte metabolism during the period of fetal zone involution. Little evidence of abnormal function in early life has been found in spite of the dramatic morphologic changes in the gland. The present paper extends these observations to include data on the capacity of young infants to respond to ACTH during the period of fetal zone involution. The response as measured by the urinary formaldehydogenic steroid excretion follows the pattern found in normal adults, but the response as measured by the sodium balance differs from that seen in adults.

Observations on three infants born of toxemic mothers, two of whom had received antepartum therapy with ACTH and cortisone, respectively, provided a few data on adrenal function in infants born of toxemic mothers and on the transplacental movement of ACTH and cortisone. Clear evidence for the placental transfer of hormones is difficult to obtain. For example, the signs of estrogen activity in the newborn infant are usually thought to result from the action of hormones acquired from the mother. While this is probably true, the question is complicated by the fact that the placenta is itself a versatile endocrine organ, producing estrogens,[3] androgens,[4] progesterone,[5] a gonadotrophin[6] and perhaps other hormones[7] as well. It is therefore often impossible to be sure of the site of origin of a hormone reaching the fetus during pregnancy. The observations in two cases in the present study bearing on the placental transfer of ACTH and cortisone were obtained from toxemic pregnancies, in which placental physiology is abnormal; the data suggest that ACTH traversed the placenta and produced measurable effects in the infant,

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TABLE 1

URINARY FORMALDEHYDOGENIC STEROID EXCRETION IN ACTH-TREATED PREMATURE INFANTS

Patients	Period			Dose of ACTH mg./24 hr./M²
	Pretherapy	ACTH therapy	Post-therapy	
Case 1 (Mo)	2.3 (3)	5.7 (14)	4.6 (7)	40
Case 2 (Ro)	0.7 (5)	4.3 (8)*		20
		2.9 (6)*		10
			1.3 (9)*	
		1.8 (11)†		10
			1.6 (9)†	
Case 3 (Ros I)	3.8 (8)	5.9 (11)		21‡
Case 5 (Ac)	1.3 (4)	5.2 (14)	2.2 (12)	30

*=1st ACTH therapy period.
†=2nd ACTH therapy period.
‡=Average dose.

Excretion of formaldehydogenic steroids by 4 premature infants before, during and after ACTH therapy. Values are averages for each period and are expressed as mg. DOC⇌/M²/24 hr. Figures in parentheses indicate number of values upon which each average is based. Case 4 is omitted because pre- and post-therapy values are not available.

while cortisone did not. Further observations are needed to confirm the observations and to show whether they are applicable to the normal placenta.

METHODS

Methods are the same as those used in the previous study.[2] ACTH made from pork pituitaries was kindly supplied by the Armour Laboratories.

RESULTS

1. Urinary Formaldehydogenic Steroid Excretion.*

ACTH-treated infants (Cases 1-5: The 5 infants treated with ACTH were developing retrolental fibroplasia. The failure of therapy in preventing progression of the disease in these cases and the manner of death of one infant during therapy has been previously reported.[8] Dosage of ACTH ranged usually from 20 to 40 mg./day given in 4 divided doses intramuscularly, but smaller doses were given for part of the time in 4 of the cases.

The urinary formaldehydogenic steroid excretion and related data in the 5 ACTH-treated premature infants are shown in chart 1.

The values rose during the period of ACTH administration and fell after its discontinuance, as shown by the average values before, during and after treatment (table 1).

In 2 individuals receiving varying ACTH dosage, steroid excretion varied in the direction of the

* The values previously reported[2] for premature infants without recognized disease and for normal male adults are:

		standard deviation
5 premature infants, 1st or 2nd day of life	0.67 mg./M²/24 hr.	0.17 mg./M²/24 hr.
7 premature infants, 10th day of life	1.17 " "	0.30 " "
9 young adult males	0.87 " "	0.10 " "

A significant rising trend after the 10th day of life in premature infants was demonstrated, but the extent and duration of the rise could not be statistically evaluated.

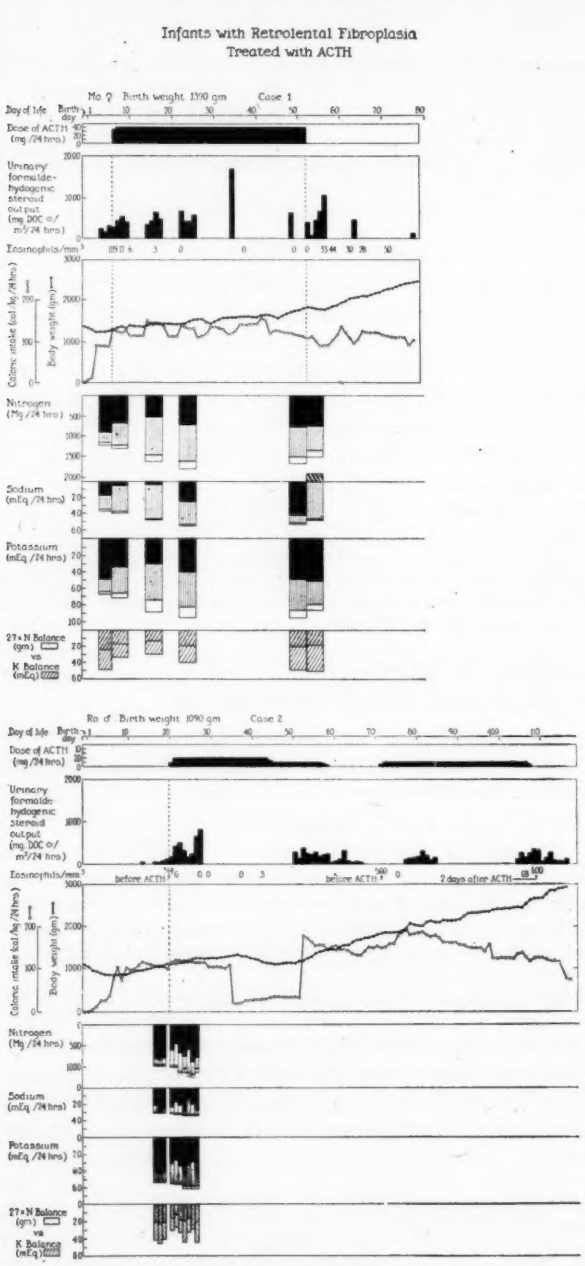
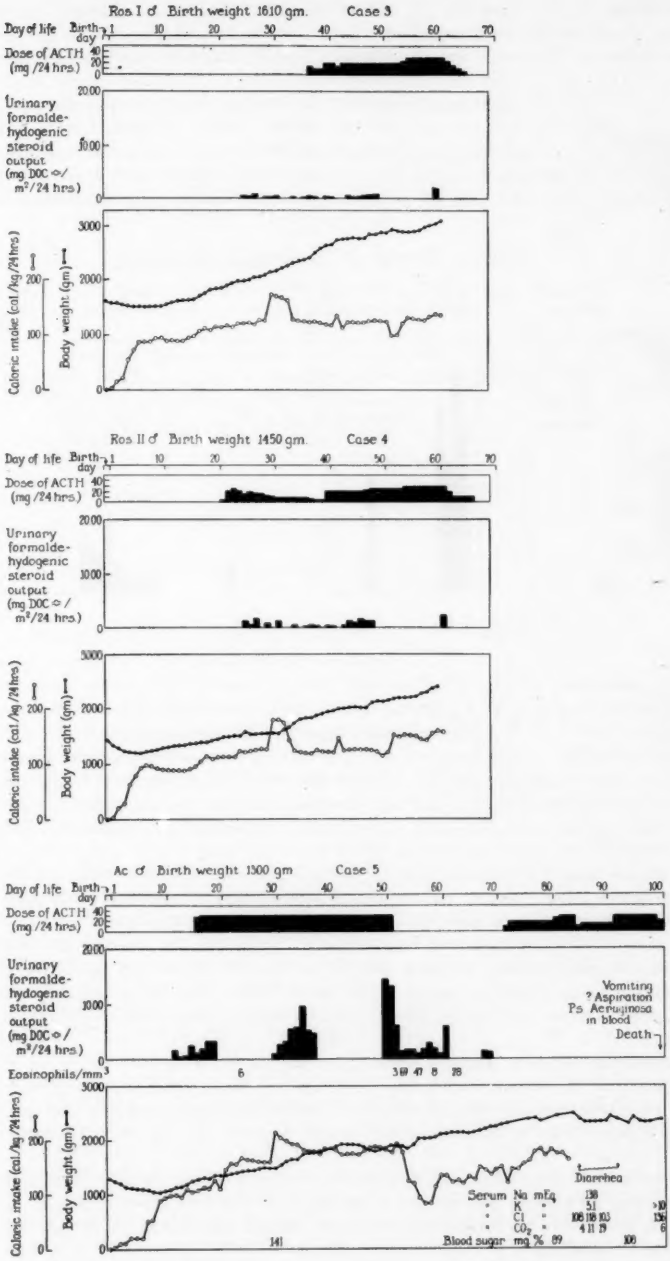


CHART 1. Urinary formaldehydogenic steroid excretion and related data.


Ros I ♂ Birth weight 1610 gm. Case 3
Day of life
Birth day
Dose of ACTH (mg /24 hrs.)
Urinary formalde-hydogenic steroid output (mg DOC eq./ m²/24 hrs.)
Caloric intake (cal./kg./24 hrs.)
Body weight (gm.)
Ros II ♂ Birth weight 1450 gm. Case 4
Ac ♂ Birth weight 1300 gm Case 5
Vomiting
? Aspiration
Ps Aeruginosa in blood
Death
Eosinophils/mm³
Diarrhea
Serum Na mEq
K
Cl
CO₂
Blood sugar mg %

change in dosage (Cases 2 and 4). The steroid excretion following discontinuance of ACTH was observed on 4 occasions (Cases 1 and 5, twice in Case 2). A sharp fall occurred on the second to the fourth day following cessation of therapy; somewhat higher values subsequently appeared on 3 of the 4 occasions.

Infants Born of Toxemic Mothers (Cases 6-8): Three infants were born spontaneously of toxemic mothers. One mother was untreated, one received ACTH 100 mg. intramuscularly daily for 9 days antepartum and one cortisone 150 mg. intramuscularly for 12 days antepartum. Formaldehydogenic steroid excretions for the infants are shown in chart 2. These infants were born of mothers with toxemia of pregnancy receiving either no antepartum hormonal therapy (Case 6) or antepartum ACTH

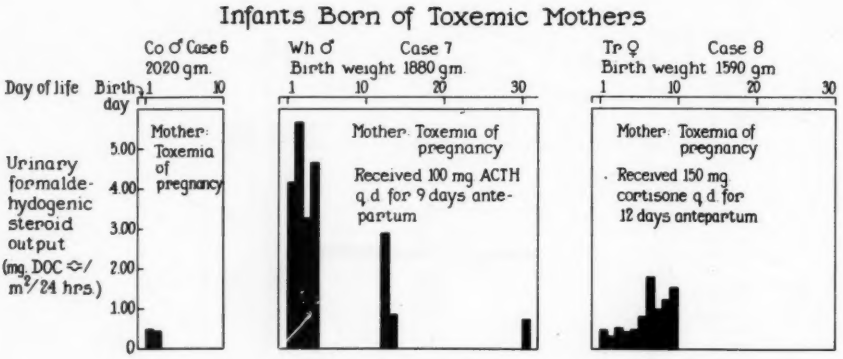


CHART 2. Urinary formaldehydogenic steroid excretion.

(Case 7) or antepartum cortisone (Case 8). The chart indicates the high urinary formaldehydogenic steroid excretion during the 1st 4 postnatal days by the infant born of the ACTH-treated mother.

The infant (Case 6) of the untreated mother appeared normal until the end of the first day of life, but during the next 2 days developed rapidly deepening jaundice, opisthotonus, pulmonary rales and cutaneous hemorrhages, and died on the third day. Blood culture contained Staph. aureus hemolyticus. The mother was Rh-positive and had a negative serologic test for syphilis. Autopsy on the infant revealed massive hemorrhages into the lungs and gastrointestinal tract. Steroid excretions for the 1st 2 days of life were 0.49 and 0.42 mg./M^2/24 hr.

The infant of the ACTH-treated mother (Case 7) appeared normal at birth but had cyanotic spells when removed from oxygen. He later was thought to have a coarctation of the aorta and subsequently developed roetrolental fibroplasia; no ACTH was administered postnatally. His formaldehydogenic steroid output averaged 4.45 mg./M^2/24 hr. during the 1st 4 days of life and was 2.90 mg./M^2/24 hr. on the 13th day. Excretion then fell on the 14th day to 0.83 mg./M^2/24 hr.

The formaldehydogenic steroid outputs of the infant born of the cortisone-treated mother (Case 8) ranged from 0.32 to 1.80 mg./M^2/24 hr. and averaged 0.87 mg./M^2/24 hr. during the 1st 10 days of life.

2. Electrolyte and Nitrogen Balance Studies.

In the graphs of the balance studies, the total length of the bars below the zero line represents intake, the clear area represents fecal excretion, vertical hatching urinary excretion, and solid black the net positive balance. Negative balances are shown with diagonal hatching and extend above the zero line.

The bottom graph in each balance study compares the N and K balances. The normal proportion of these elements in protoplasm is about 2.7 mEq. K/gm. N.[5] In these graphs the gm. N has been multiplied by 2.7 so that the bars should be of equal length when all K and N retained are used to form normal protoplasm.

Balance studies for Na, K and N were carried out in 2 ACTH-treated infants (chart 1, Cases 1 and 2). Positive balances for Na, K and N were found during the first, or pretreatment, balance period in both cases.

In Case 1, in which the infant received ACTH 40 mg./24 hr., these became smaller but remained positive during the second and third balance periods, which ended after 12 days of ACTH therapy. All balances increased in the fourth and fifth balance periods; in the fifth period, which ended after 46 days of ACTH therapy, the N balance approached and the K balance reached the pre-therapy level. Na retention before therapy was 1.7 mEq./24 hr.; after the decrease in the second and third periods, it rose in the fourth period to 2.6 mEq./24 hr. and in the fifth period to 4.3 mEq./24 hr. In the 4 day balance period after discontinuance of ACTH, N and K balances showed little change, but there was a sudden outpouring of Na with a negative balance of −0.91 mEq./24 hr.

In Case 2, where the patient received ACTH 20 mg./24 hr. during the second part of the balance study, no striking change in Na, K or N balance occurred with ACTH therapy, though retentions for each were slightly diminished.

A balance study in the infant born of the cortisone-treated mother is illustrated in chart 3. It is similar in all regards to one previously reported and discussed in a normal premature infant.[3]

3. Miscellaneous Observations During and Following ACTH Therapy.

Administration of ACTH was usually followed by blanching of the skin at the injection site lasting 4 to 6 hr. and generalized mottling of the skin of shorter duration. Minimal transient edema was encountered in some of the patients. Glycosuria and hyperglycemia were found in each of the 3 cases tested and disappeared after cessation of therapy in 2 cases; the third patient (Case 5) died while receiving ACTH. A dusky gray-blue color to the skin appeared in each case during therapy and subsequently faded. Eosinophile counts made in 3 cases (Cases 1, 2, and 5) fell during ACTH usually to values below 18 cells/mm^3; in Cases 1 and 5 low values were still found 20 and 12 days, respectively, after discontinuance of the drug, but in Case 2, the eosinophile count was at normal levels on the 2nd day following cessation of therapy. Weight gains were diminished or ceased during ACTH therapy; in Case 5 the caloric intake was increased to 171-214 cal./kg./day for 24 days in the first ACTH period in an effort to maintain a normal weight gain. At first the infant's weight increased with the increased caloric intake but later remained approximately stationary in spite of the continued high caloric regimen. Slow weight gain was resumed at a normal caloric intake immediately after discontinuance of ACTH. An error in compounding the formula in Case 2 led to ingestion of extremely low caloric intakes (20 to 34 cal./kg./day) over a period of 17 days; the error was not recognized until several days after it had been corrected; the sudden change, unknown at the time, from 32 cal./kg./day to the intended formula of 178 cal./kg./day was not attended by any digestive disturbance. Edema was noted just before the change and for about a week thereafter, and may have been associated with the preceding period of inanition. Weight gain occurred when the formula was increased and continued as the edema disappeared.

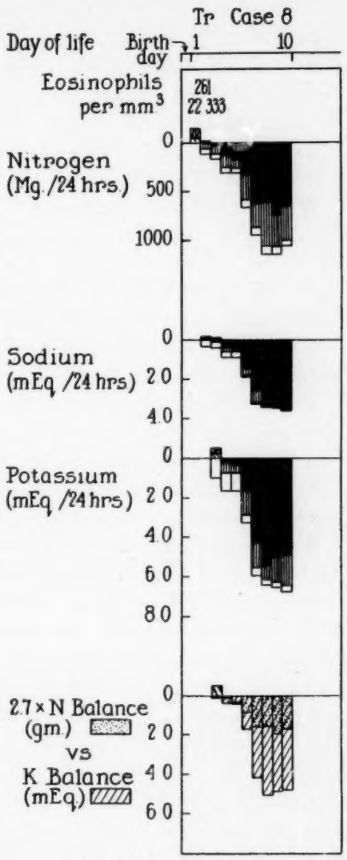


CHART 3. Nitrogen, sodium and potassium balance data in infant born of toxemic mother treated antepartum with cortisone. (Balance data are in all regards similar to those obtained in premature infants without recognized disease.[1])

DISCUSSION

The level of urinary formaldehydogenic steroid excretion increased during the periods

of administration of ACTH to the infants. Part of the rise was probably due to the increasing age of the infants, since excretion values rose with age in untreated premature infants. Part of the rise, however, was thought to result from ACTH stimulation, since the average excretion level fell promptly after discontinuance of therapy. These premature infants were therefore capable of responding to ACTH with an increased urinary excretion of formaldehydogenic steroids. The associated eosinopenia indicated that the increased excretion reflected increased production.

When ACTH was discontinued, a fall in steroid excretion occurred on the second to the fourth day on each of the four occasions studied; slightly higher values were found after the fall on 3 of the 4 occasions. The fluctuation suggested that pituitary inhibition had occurred during the period of ACTH administration and that a short time was required for readjustment following discontinuance of the drug. The rapidity with which stable levels were achieved after prolonged periods of ACTH therapy indicated the effectiveness of the homeostatic mechanisms controlling the pituitary-adrenal system.

These findings suggested that the adrenals in the newborn infants had a functional reserve and were capable of responding to either an increase or a decrease in the trophic stimulus by an appropriate change in steroid production. This pattern of response is the same as that normally found in the adult and indicates that this aspect of adrenal function was not measurably disturbed during the period of adrenal fetal zone involution.

While steroid production in infants responds to ACTH in the same manner as in adults, the behavior of Na appears to be dissimilar. Normal adults tend to retain Na under the influence of ACTH, but Klein[9] found that young infants behaved differently and responded with diminished retention. The electrolyte balance studies in Case 1 confirmed Klein's findings and showed that during the first days of ACTH administration less Na was retained than during the control period. Klein observed no tendency ultimately to retain Na under continued ACTH therapy, but his periods of administration did not exceed 10 days. The long-continued administration of ACTH in Case 1 was associated with rising Na retention by the fourth balance period, or after 16 days of ACTH therapy. The Na balance subsequently exceeded the pretreatment retention as would be expected in the adult. The early diminished Na retention may explain why infants with hypoadrenalism may become worse when treated with ACTH. This abnormal response cannot at present be associated with any of the anatomic changes in the adrenal in early life, and the cause is unknown. A somewhat similar situation exists in adults with Cushing's disease,[10] in whom the administration of desoxycorticosterone causes a sodium diuresis instead of the usual retention. No basic mechanism associating these two similar phenomena is known at present.

The electrolyte balance studies in Case 2 showed little change with the administration of ACTH to the subject. The difference between the response in Case 1 and Case 2 may be due to the difference in ACTH dosage, which was 40 and 20 mg./24 hr., respectively.

The relationship of K to N retention is illustrated in the bottom graph of each balance study. The N balance in grams is multiplied by the factor 2.7, which represents approximately the number of grams of N per mEq. of K in normal protoplasm. The graph shows that approximately twice as much potassium is apparently retained as is needed in protoplasm formed from the retained N. This discrepancy was noted in the balance studies on normal premature infants and discussed previously.[2] It has been found also by other investigators and is best explained by Gamble et al.,[11] who showed that skin losses for K, unmeasured in the usual balance study, approximately account for the discrepancy.

The two infants (Cases 7 and 8) born of hormone-treated toxemic mothers present an interesting contrast. The infant (Case 8) of the cortisone-treated mother had normal postnatal urinary formaldehydogenic steroid excretions. The infant (Case 7) of the ACTH-treated mother had elevated steroid excretions for four days after birth; a single value on the 13th day was also elevated. A return to levels usually found in untreated infants occurred on the 14th day. The early postnatal values were higher than any found in a normal infant at a corresponding time of life. The observation suggests that cortisone did not cross the placenta in sufficient amount to influence the infant's postnatal steroid excretion, but that ACTH administered prenatally reached the fetus and stimulated the adrenals. The ACTH employed was a protein, and the ability of proteins to cross the placenta in the last trimester is established by passive antibody transfer. The stimulating effect of ACTH persisted in the postnatally treated infants for only 1 to 3 days after discontinuance of therapy. The reason for the more prolonged elevation in steroid excretion in Case 7 is unknown. The toxemic pregnancy itself is probably not responsible; since no increase was found in Cases 6 and 8, in which the patients were also born of toxemic mothers. Moreover an electrolyte balance in Case 8 was similar in all respects to one obtained in a normal infant. Kinnunen and Niemineva[12] have found that the adrenals of infants born of toxemic mothers are normal by weight; these findings also indicate that the adrenals in such infants are not measurably abnormal.

Because ACTH has been used in the treatment of retrolental fibroplasia, it is of interest that an infant whose mother was treated antepartum with the drug ultimately developed the disease (Case 7).

Summary

The urinary formaldehydogenic steroid excretion was measured in 5 ACTH-treated premature infants and in 3 premature infants born of toxemic mothers. One of these toxemic mothers received no therapy, one received ACTH antepartum, and one cortisone antepartum. Na, K and N balance studies were conducted in three of the above infants.

Steroid excretion rose during ACTH administration and fell 2 to 4 days after discontinuance of ACTH therapy. The fall was followed by a moderate rise, or rebound, in some cases. These findings indicate that the adrenals of young infants have a functional reserve and are capable of responding to either an increase or a decrease in the adrenocorticotrophic stimulus by a corresponding change in steroid production. This response resembles that seen in normal adults and is further evidence that this aspect of adrenal function is not impaired during involution of the fetal adrenal cortex.

ACTH administration in one infant produced an increase in sodium excretion during the first 16 days of therapy. This response is the opposite of that usually found in normal adults, and confirms a similar previous finding reported by Klein.[9] Under continued ACTH therapy, the infant ultimately retained Na as does the normal adult. The cause for this early abnormal response is unknown, but it resembles one seen in adults with Cushing's disease, in whom desoxycorticosterone induces a loss of sodium.

The infant born of the cortisone-treated toxemic mother had normal postnatal urinary steroid values; the infant born of the ACTH-treated toxemic mother had unusually high postnatal values. These observations suggest that cortisone failed to cross the placenta in sufficient quantity to influence steroid excretion of the infant, but that ACTH administered to the mother reached the fetus and stimulated his adrenals.

ACKNOWLEDGMENT

Grateful acknowledgment is made to Mr. Justin L. Russel for technical assistance, and to the nurses of the Bellevue Hospital Premature Infant Unit, in particular to Miss Martha Roberts and Miss Eileen Hasselmeyer, for nursing care and the collection of specimens.

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SPANISH ABSTRACT

Función Cortical de las Suprarrenales en Niños Prematuros

II. Niños Tratados con ACTH y Niños Nacidos de Madres Toxémicas

En un artículo previo el autor reportó los datos obtenidos acerca de la excresión de esteroides y del metabolismo de los electrolitos durante el periodo de involución de la zona fetal de las suprarrenales encontrando escasa evidencia de función anormal a pesar de los cambios morfológicos marcados de la glándula. En esta comunicación amplía dichas observaciones incluyendo datos acerca de la capacidad del lactante pequeño para responder al ACTH durante el periodo de involución de la zona fetal.

El estudio comprendió la determinación de la excreción de los esteroides urinarios formaldehidogénicos en 5 niños prematuros tratados con ACTH y en 3 niños prematuros nacidos de madres con toxemia. Una de estas madres intoxicadas no recibió terapeútica, la otra recibió ACTH y la última cortisona, ambas antes del parto. En los 3 niños nacidos de estas madres toxémicas se hicieron balances de Na, K y N.

La excreción de esteroides se elevó durante la administración de ACTH y cayó entre los 2 y los 4 días después de suspender la terapia en ACTH. La caída fué seguida de una elevación moderada "rebound," en algunos de los casos. Estos hallazgos indican que las suprarrenales de los lactantes pequeños tienen una reserva funcional y son capaces de responder, ya sea a un aumento o a una disminución del estímulo adrenocorticotrópico, con un cambio correspondiente en la producción de esteroides. Esta respuesta se semeja a la que se ve en los adultos normales y es una prueba más de que durante la involución de la corteza suprarrenal este aspecto de la función de la glándula no está interferido.

La administración de ACTH en uno de los lactantes produjo un aumento en la excreción de sodio durante los primeros 16 días de terapéutica. Esta respuesta es lo opuesto de lo que usualmente se observa en adultos normales y confirma un hallazgo similar previamente reportado por Klein. Bajo terapia continua con ACTH el niño finalmente retuvo Na como lo hace el adulto normal. La causa de esta respuesta temprana anormal es desconocida, pero se parece a la vista en adultos con enfermedad de Cushing en quienes la desoxicorticosterona induce una pérdida de sodio.

El niño nacido de la madre toxémica tratada con cortisona tenía cifras postnatales normales de esteroides urinarios y el niño nacido de la madre toxémica tratada con ACTH tenía cifras postnatales desusualmente altas. Estas observaciones sugieren que la cortisona no atravesó la placenta en cantidad suficiente para influir la excreción de esteroides del lactante pero que el ACTH administrado a la madre llegó al feto y estimuló sus suprarrenales.

477 First Avenue

ACTH IN THE TREATMENT OF ERYTHROBLASTOSIS

II. Progress Report

By Lt. Colonel Leo J. Geppert, M.C., Lt. Colonel Joseph H. Akeroyd, M.S.C., and Colonel John W. Simpson, M.C.
Fort Sam Houston, Texas

A PRELIMINARY report on the use of adrenocorticotrophic hormone (ACTH) in the treatment of erythroblastosis has been published.[1] The present communication summarizes further experience with this form of treatment. These patients were treated at Brooke Army Hospital and were dependents of military personnel from the immediate vicinity of San Antonio, Texas. Due to these restrictions on case selection only a normal distribution of Rh-sensitized obstetric patients was encountered as expected (1/250 deliveries). Because of the small number of patients available for study it was considered justifiable to forego the obvious advantages of using an alternate control series treated by other methods and confine the investigations to observations of infants treated with ACTH according to a uniform plan.

Material and Methods

When a patient registered with the prenatal clinic, complete blood typing was included in initial examination. If she was found to lack D-agglutinogen (even though C- or E-positive), blood types of husband and children were determined as an aid in predicting the genotype of the fetus. Serum of all D-negative patients was tested for residual Rh antibodies. Qualitative and quantitative tests designed to identify agglutinins, agglutinoids and cryptagglutinoids were used.[2] Patients developing atypical antibodies were followed carefully during their confinement.

At time of delivery red cells from cord blood were immediately examined for adsorbed antibodies using Coombs' anti-human-globulin serum of known potency.[3] If there was 3+ or 4+ agglutination ACTH therapy was considered. Clinical condition of the infant, nature of amniotic fluid, vernix and placenta, amount of anemia, differential blood count, serum bilirubin and type of antibody developed in the mother were all considered in making a decision as to the necessity for active therapy. Infants selected for treatment were given ACTH* 12.5 mg. immediately after birth and 6.25 mg. every 6 hr. thereafter (tables 1 and 2).

Pertinent serial determinations were made on treated infants. Values were recorded for Coombs' test, Hgb, RBC count, WBC count, normoblasts, eosinophiles/m^3, serum bilirubin and clinical condition. Factors considered in evaluating therapeutic response were hepatosplenomegaly, jaundice and toxicity.

If the Coombs' developing test on cord blood was only 1+ or 2+ and clinical condition of infant, was satisfactory, no treatment was given. This decision was made on 7 occasions during this study period. Although each of these infants developed mild erythroblastosis none became severely jaundiced despite presence of positive maternal titres, mildly positive developing tests and nucleated RBC varying from 14 to 26%. Hemolysis in one case did require transfusion before discharge from hospital.

From the Pediatric, Laboratory and Obstetrical Services, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

ACTH for this study was provided through the courtesy of Harley E. Cluxton, Jr., M.D., Director of Medical Research, The Armour Laboratories.

(Received for publication June 19, 1952.)

* Acthar®, Armour & Co.

TABLE 1

Erythroblastotic Infants Treated with ACTH—Family History

No.	Blood Types			Mother Transfused	Previous Pregnancies			Maternal Titre at Delivery		
	Patient	Mother	Father		No.	Erythroblastotic	Died*	Saline	Albumin	Developing
1	O CDe/cde	O cde/cde	O CDe/CDe		4	1	1 K	Neg.	Neg.	1:256
2	AB CDe/cde	A cde/cde	B CDe/CDe		5	1		1:2	1:32	1:256
3	A CDe/cde	A cde/cde	O CDe/cde	x	3			1:8	1:64	1:32
4	A CDe/cde	B cde/cde	A CDe/?	x	1			Neg.	Neg.	1:128
5	B cDe/cde	O cde/cde	B cDE/?		2			1:2	1:8	1:32
6	O CDe/cdE	O cdE/cde	A CDe/cde		4			Neg.	Neg.	1:32
7	O CDe/cde	A cde/cde	A CDe/cDE		3	2		1:32	1:32	1:32
8	A CDe/cde	A cde/cde	A CDe/cde	x	6		1 M	1:64	1:512	1:512
9	O cDe/cde	O cde/cde	O CDe/cDE		1	1		1:64	1:64	1:64
10	O CDe/cde	O cde/cde	O CDe/cde	21	2		2 M	Neg.	1:256	1:256
11	O CDe/cde	O cde/cde	O CDe/CDe		1			Neg.	1:64	1:64
12	O CDe/cde	O cde/cde	O CDe/?		1			Neg.	1:64	1:256
13	O cDE/cde	O cde/cde	O CDe/cDE	x				Neg.	1:64	1:32
14	A cDE/cde	A cde/cde	A cDE/cde		3		1 M 1 S	Neg.	1:32	1:32
15	O CDe/cde	O cde/cde	A CDe/cde		3			Neg.	1:4096	1:4096
16	A CDe/cde	A cde/cde	B CDe/CDe		3	1		1:8	1:64	1:32
17	A CDe/cde	A cde/cde	A CDe/cDE		2	1				1:128
18	A cDe/cde	A cde/cde	O CDe/CDe		2		1 A	1:32	1:64	1:32
19	O cDE/cde	O cde/cde	O cDE/cde		4		1 M 1 S	Neg.	1:8	1:2
20	A cDe/cde	O cde/cde	A cDe/cde		2				1:8	1:32

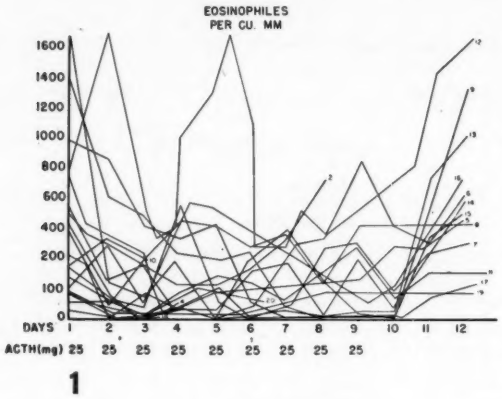
* K—Kernicterus.
M—Miscarriage.
S—Stillborn.
A—Abortion.

TABLE 2

Erythroblastotic Infants Treated with ACTH—Initial Values

No.	Wt. (gm.)	Liver (cm.)	Spleen (cm.)	Eosinophiles	Coombs' test	WBC count	% Normoblasts	Hgb./100 cc.	RBC count	Jaundice—Days			Serum Bilirubin—Days			Died
										1	3	8	1	3	8	
1	3183	1.5	3		3+	100,000	17	6.5	1.6	3+	4+	+	4.0	24.0	10.0	
2	4224	3	3	460	4+	80,000	50	8.0	2.0	+	0	0	4.0	4.0		
3	3224	3	1	1385	3+	67,000	52	7.0	2.0	+	+	0	3.0	1.6	0.8	
4	2977	2	2	675	3+	25,000	33	18.0	4.6	+	4+		4.6	27.9		3rd day
5	2778	0	0	175	3+	21,300	30	14.0	3.5	0	+	0	5.0	9.6		
6	3884	3	1	768	3+	15,100	35	14.5	5.0	+	3+	0	10.0	20.0	0.8	
7	3487	3	1	132	3+	37,000	14	19.0	3.3	+	0	0	3.4	3.0	2.0	
8	3742	3	2	38	4+	14,250	5	16.5	5.6	+	2+	0	3.0	11.4	0.8	
9	3374	5	3	950	2+	30,150	0	8.5	2.3	+	+	0	4.0	5.6		
10	2402	4	1	168	3+	114,000	75	10.0	2.7	0	2+		4.0	18.0		3rd day
11	3423	2	1	50	3+	40,000	2	22.5	6.2	0	0	0	4.4	7.0	0.8	
12	2976	4	2	2025	2+	73,500	68	14.8	5.1	+	2+	+	1.3	16.0	8.4	
13	3125	2	2	563	2+	19,300	12	16.0	4.4	0	2+	0	5.2	20.8	2.2	
14*	2863	2	1	413	2+	15,800	28	10.0	2.3	0	+	+	4.0	12.1	8.8	
15	2466	0	0	50	4+	20,300	44	7.0	2.2	+	2+	+	2.4	22.0	3.0	
16*	3345	0	0	100	3+	20,550	12	14.5	4.9	0	+	0	3.6	4.8	1.6	
17*	1871	4	2	25	3+	31,600	1	10.5	2.2	2+	+	+	5.6	3.5	1.4	
18*	2820	3	0	84	+	20,700	19	13.5	4.3	+	4+		10.0	36.0		3rd day
19*	1744	2	0	88	3+	13,600	4	18.5	4.4	+	3+	0	2.4			
20	3374	1	0	94	3+	21,000		14.8	4.4	+	+	0	6.3	7.0	0.6	

* Mother received ACTH prior to delivery.



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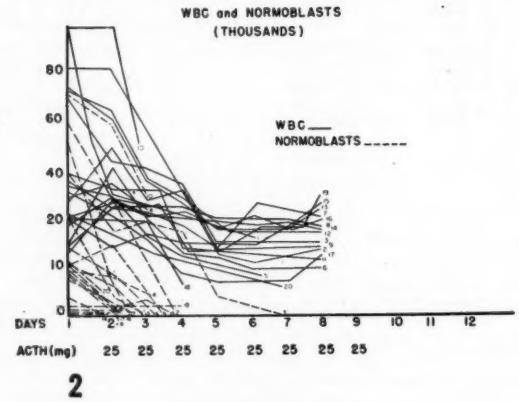

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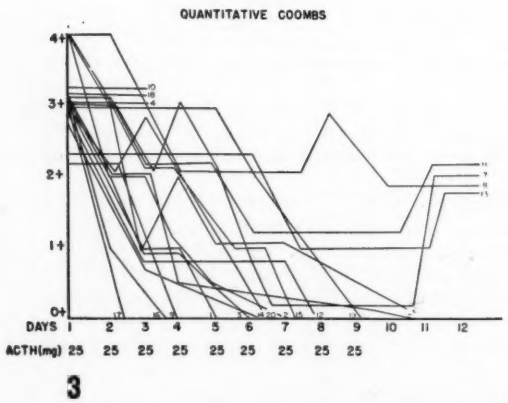

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FIGS. 1-3. Line graphs of daily observations on 20 erythroblastotic infants treated with ACTH. 1. Eosinophile counts. 2. Quantitative Coombs' test. 3. Nucleated cells/cmm.

Observations

Duration of Therapy

ACTH therapy was continued until Coombs' test was negative for 2 successive days. Mean period of therapy was 8.5 days. Only 3 patients were treated more than 12 days. Treatment in one of these patients was continued because Coombs' test remained positive, and was resumed in the other 2 because the test became positive and hemolysis occurred when ACTH therapy was discontinued.

Eosinophile Response

Eosinophile counts/m^3 were done every morning 4 hr. after an injection of ACTH (Fig. 1). A few patients showed no adrenal response as measured by this test. Majority, however, showed a rapid fall in 1st 24 hr. and count remained low until ACTH therapy was discontinued. There was usually a prompt increase in eosinophile count following discontinuation of ACTH therapy. Dose of ACTH was increased in one patient when a significant rise in eosinophile count occurred indicating possible ACTH escape.

Quantitative Coombs' Test

Although Coombs' test remained faintly positive as long as 24 days in one case, trend was toward a rapid reversal during the 1st 4 days paralleling the eosinophile count (Fig. 2). In Case 8 no response to ACTH was observed as manifest by daily mean 11-oxysteroid urine value of 0.2 mg. Coombs' test remained strongly positive in this patient for 18 days and weakly positive for an additional 6 days. The Coombs' test in Case 7 became negative on 5th day and ACTH therapy was discontinued on 10th day. Twenty-four hours later Coombs' test again became strongly positive. Serum bilirubin rose to 12 mg./100 cc. blood and patient became clinically jaundiced. Fecal urobilinogen which was previously less than 10 mg./day reached levels of 70 mg./24 hr. on 15th day. Therapy with ACTH, reinstituted on 17th day, was followed by a rapid reversal of Coombs' test and cessation of hemolysis. Serum bilirubin was normal on 22nd day. A similar but less marked pattern, not requiring retreatment, was followed by Cases 11 and 13.

Nucleated Cells per Cubic Millimeter

Number of nucleated cells/m^3 dropped to normal by 5th day and remained fairly stationary thereafter. This decrease in number of nucleated cells was due chiefly to a disappearance in absolute numbers of nucleated red cells (Fig. 3). Curves are similar to those for eosinophilic response. Platelet counts show a rising trend.

Hemoglobin and Red Blood Cell Count

Values for Hgb and RBC count increased, reaching a peak on 4th day (Figs. 4 and 5). They invariably dropped after discontinuation of ACTH therapy. Both increase and decrease do not seem related to hemolysis and must be due to some other effect of ACTH therapy on mobilization of red cells.

Clinical Jaundice and Serum Bilirubin

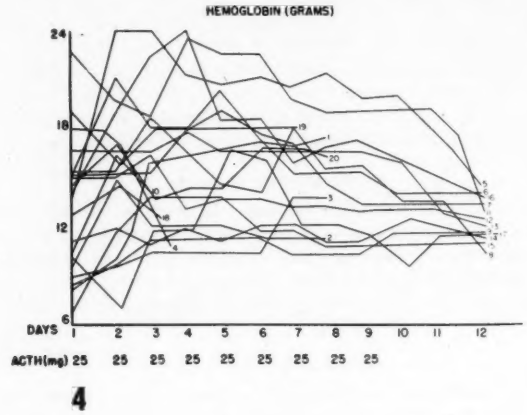
Daily reticulocyte counts were done on Cases 3, 5 and 14. Counts showed a progressive decrease from a mean of 32% to 4.8% on 10th day. Hemolysis was certainly not completely prevented as was manifest by jaundice in almost all patients. Serum bilirubins reached their height on 4th day (Fig. 6).

Weight

Weight remained stationary during ACTH therapy. Rapid weight gain followed discontinuation of treatment. Although many infants were apparently more hungry than usual while receiving ACTH therapy there was no absolute increase in caloric intake.

Mortality

Total number of cases is so small that mortality figures are not statistically significant. Mortality figures in this series compared to the previous 10,000 deliveries[4] are included as a matter of interest. There were no major changes in obstetric population or management of obstetric patients during these 15,000 deliveries. Early induction of labor was never practiced in the management of Rh-sensitization.



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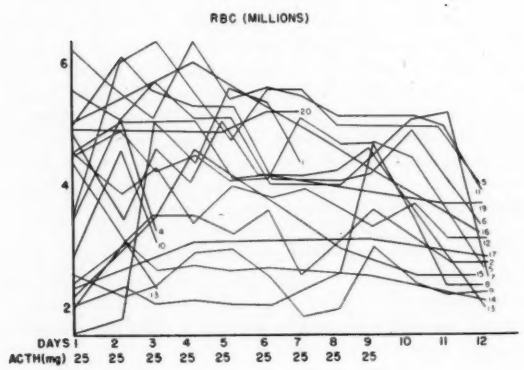

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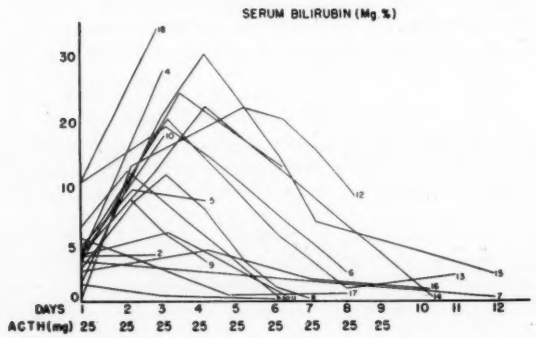

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FIGS. 4-6. Line graphs of daily observations on 20 erythroblastotic infants treated with ACTH. 4. Hemoglobin determinations. 5. Red blood cell counts. 6. Serum bilirubin determinations.

	5,000 Deliveries 1944-1946 Repeated Trans.	5,000 Deliveries 1947-1949 Exchange Trans.	5,000 Deliveries 1950-1952 ACTH Therapy
Number	19	16	20
Deaths	9	3	3
Mortality	47%	18%	15%
Mild Cases Not Treated	6	6	7
Over-all Mortality	36%	13.6%	11.1%
Deaths/1,000 Births	1.8	.6	.6

Cases 4, 10 and 18 were fatal. In Case 4 severe jaundice, hematemesis and hematuria developed suddenly and patient died on 3rd day. Kernicterus was discovered at autopsy. Case 10 was a premature infant who died from respiratory failure on 3rd day of life. The clinical course was that of hyaline atelectasis. The only notable autopsy finding was resorption atelectasis. Infant No. 18 suddenly developed severe abdominal distention and respiratory difficulty on the 3rd day and died despite immediate transfusion. An electrocardiographic tracing showed no evidence of hypokalemia. Autopsy was not revealing. Although the eosinophile counts on the day of death of these 3 infants were 50, 200 and 25, respectively, indicating adrenal response, the Coombs' test stayed strongly positive until death on the 3rd day. Hemolysis was also indicated in all 3 patients by a rapid rise in serum bilirubin with a corresponding fall in hemoglobin determinations and RBC counts. No surviving patient has evidence of kernicterus.

Toxic Reactions to ACTH

Undesirable metabolic alterations were not observed in any patient receiving the arbitrarily chosen dosage of ACTH 25 mg./day (60 mg./sq. m. body surface/day). Potassium chloride/1 gm. was given orally daily. When the dose of ACTH was increased to 45 mg./24 hr., because of poor eosinophile response, one patient developed electrocardiographic evidence of hypokalemia. In addition to ACTH each of these infants received benadryl®, 6 mg. 3 times a day, because this had been a part of the regime for the previous series.

Since ACTH is reputed to increase susceptibility to infection, penicillin and streptomycin were administered routinely to these infants until ACTH was discontinued. Vitamin K was also given to each patient and vitamin C 200 mg. was given parenterally daily.

Four of the infants had a peculiar reaction to pork ACTH. Following the injection severe blanching occurred in an area 4 cm. in diameter which persisted for 1 hr. This was followed by purplish discoloration. The reaction disappeared after 8 hr. and was not followed by the formation of hematoma, abscess or slough. The reaction was produced by several different lots of ACTH although the same lots produced no such reaction in adults or older children. Armour & Co. then provided the authors with sheep ACTH (Acthar-C®). With this product there were no such reactions. When the sheep product was temporarily unavailable, pork ACTH was continued uneventfully in one case except for local reaction.

Discussion

As Pickles has stated, in erythroblastosis "The most vital factor is the institution of treatment as soon as possible after birth."[5] Since some newborn infants seem refractory to ACTH and in almost all several days are required to obtain a fall in eosinophile count, a reversal of the Coombs' test, and an increase in 17-ketosteroids, 11-oxysteroids or both, more rapid results might be obtained by using larger initial doses of ACTH or by administering the hormone intravenously until the Coombs' test becomes negative and the eosinophile count approaches zero. Early in this study Dr. John R. Mote of Armour Laboratories suggested that ACTH be given intravenously in a solution of glucose by the umbilical catheter technic.[6] Because of the severe local reaction to pork ACTH described this suggestion was not followed. The local reaction has not been encountered with sheep ACTH and the intravenous method of administration might be attempted with this preparation. The mothers of Patients No. 14, 16, 17, 18 and 19 received ACTH for a minimum of

five days prior to delivery. The only detectable effects on the infants delivered of these mothers were low initial eosinophile counts, low total white cell counts, and a very low absolute number of circulating nucleated red cells.

Four additional infants were studied who had clinical erythroblastosis without demonstrable antibodies in either mother or child (negative Coombs' test). Their courses with ACTH therapy were similar to those of the infants with proved Rh-adsorbed antibodies.

Theoretically, but not necessarily, cortisone might be substituted for ACTH. It was not chosen originally because of the lag between time of administration and demonstrable effect of intramuscular cortisone. A suitable product for intravenous use which would obviate this objection may soon be available.[7] Before sheep ACTH was available, intramuscular cortisone was used for two days on one patient who had a reaction to pork ACTH. The results were similar to those obtained with ACTH, but the response was slower.

So that only the effect of ACTH on serial observations might be judged, no blood transfusions were given to these infants during the period of ACTH administration even though the initial hemoglobin determinations were as low as 7 gm. Sufficient blood to bring the hemoglobin to normal was given to Patients No. 3, 6, 7, 8, 9, 12, 13, 14, 15 and 20 after the Coombs' test had become negative and ACTH had been discontinued. (Average amount of blood 125 cc.) Red blood cell counts having once been brought to normal, no infant has required further transfusions.

A more desirable method of treatment might be the institution of ACTH at birth followed by exchange transfusion for only those infants who show an alarming rise in serum bilirubin or a persistent strongly positive Coombs' developing test.

Summary

Twenty erythroblastotic infants were treated with ACTH. Immediately after delivery 12.5 mg. were given and 6.25 mg. every six hours thereafter for a median period of 8.5 days.

These infants showed a delayed adrenal response as measured by a fall in the eosinophile count by the third day.

As indicated by the reversal of the Coombs' test there was a sharp drop in the degree of sensitization of red cells in a shorter period than would have been expected naturally.[8]

The nucleated cell counts decreased to normal ranges by the fourth day chiefly because of the disappearance of erythroblasts.

Red blood cell counts and hemoglobin determinations showed a tendency to rise during the period of ACTH administration and an invariable decrease when ACTH was discontinued.

Hemolysis was certainly not completely prevented since most patients became clinically jaundiced and a concurrent rise in serum bilirubin was demonstrable.

Four infants who had clinical erythroblastosis without demonstrable antibodies (negative Coombs' test) were treated with ACTH and responded in a similar manner.

The Coombs' test became strongly positive in one patient after ACTH was discontinued on the tenth day. Serum bilirubin rose to 12 mg./100 cc. blood and the patient became clinically jaundiced. Fecal urobilinogen increased to 70 mg./24 hours on the fifteenth day. Administration of ACTH was resumed on the seventeenth day followed by a reversal of these processes.

Antibiotic therapy was added to the study regime because of the possibility that ACTH may enhance infection in the newborn infant.

A peculiar local reaction to pork ACTH was not noted with sheep ACTH.

Three patients died, all on the third day. One of these patients was found to have kernicterus at autopsy. No surviving patient has any evidence of kernicterus.

A much larger series will be required to demonstrate any effect on the mortality rate of erythroblastosis.

Seven infants with mild erythroblastosis were not treated because the potential dangers of ACTH were considered to carry more risk than their state of the disease.

Several modifications of the treatment regime used in this study are suggested.

Conclusions

These objective serial determinations as reported suggest that ACTH does alter to some degree the immunologic and hematologic responses expected in untreated erythroblastotic infants.

Addenda

The treatment of erythroblastosis with ACTH has also been evaluated according to the same plan at several other Army hospitals. Their serial observations reported to the authors do not differ significantly from trends shown by patients treated at Brooke Army Hospital. Mortality figures are as compiled below:

Hospital	Walter Reed Army Hospital	Fitzsimons Army Hospital
Pediatrician	O. C. Bruton	B. H. Berrey
Obstetrician	H. L. Riva	E. N. Akers
No. of Deliveries	1,593	2,902
Rh-Sensitized Women	11	?
Rh-Negative Infants	3	?
Erythroblastotic Infants Not Treated	2	?
Erythroblastotic Infants Treated	6	7
Deaths	0	1

Smaller series with no deaths were reported by R. C. Biehusen, Madigan Army Hospital, P. A. Bischoff, Fort Hood Army Hospital, and H. L. Guard, 97th General Hospital.

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Spanish Abstract

Tratamiento de la Eritroblastosis con ACTH

Esta comunicación presenta la experiencia de los autores con el empleo de ACTH en el tratamiento de la eritroblastosis. A 20 niños se les administraron 12.5 miligramos al nacer y en adelante 6.25 miligramos cada seis horas por un período medio de 8.5 días.

Los resultados observados fueron los siguientes: respuesta retardada de las adrenales al tercer día; brusca disminución de la sensibilización de los eritrocitos en un período más corto del esperado; normalización de la cuenta de glóbulos rojos nucleados alcuarto día, por desaparición de eritroblastos; tendencia a elevación de las cifras de glóbulos rojos y de la hemoglobina mientrasse administraba el ACTH y descenso de los mismos al suspenderlo; no prevención de la hemolisis, y por último, reacción local especial al ACTH porcino que no se observó con el de cordero.

Cuatro niños con eritroblastosis clínica y la prueba de Coombs negativa respondieron en igual forma al tratárseles con ACTH.

Tres de los niños fallecieron, todos al tercer día; uno de ellos tuvo lesiones de kernicterus (los casos que han sobrevivido no han presentado manifestaciones del mismo).

Se emplearon antibióticos para prevenir infecciones que pudieran ser favorecidas por el empleo del ACTH.

Los autores consideran que el ACTH altera en cierto grado las respuestas inmunológica y hematológica observadas en niños con eritroblastosis, no tratados, pero que se necesitan más estudios para determinar el efecto de esta droga sobre la mortalidad de los niños con el padecimiento.

Brooke Army Hospital

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Symposium

HEARING, SPEECH AND READING DIFFICULTIES IN CHILDREN

JOHN E. BORDLEY, M.D., Baltimore, *Chairman;* WILLIAM G. HARDY, M.D., Baltimore; MIRIAM PAULS, M.D., Baltimore; HARLAN BLOOMER, M.D., Ann Arbor, Mich.; A. D. RUEDEMANN, M.D., Detroit; PATRICIA J. SPAULDING, Detroit

INTRODUCTION

JOHN E. BORDLEY, M.D.

This afternoon a group of specialists in the communicative skills is to present a comprehensive review of those facts in their particular fields that concern themselves with the practice of pediatrics. Such a presentation would seem to offer 3 categories of subject matter. These fall chronologically in the developmental pattern of the growing child.

They are among the most important factors in the normal intellectual integration of the child. The 3 categories I refer to have to do with the difficulties of hearing, speech, and vision of young children. Any interference with the child's ability to hear normally, acquire speech or learn to read, be such interference physical or psychologic, it will reflect itself in the subsequent development of that child. Today the speakers on your Symposium have been asked individually or jointly to answer the 5 following questions:

1. How does the handicap in your particular field affect the child's intellectual and social development?
2. What are the warning signs of such a handicap?
3. What signs may the child present to the pediatrician to make him reasonably suspect of such a handicap?
4. What has been developed in your social field to correct such a handicap?
5. What prognosis can be offered to the family in the event rehabilitation is undertaken?

We have on the program 5 speakers. Dr. William G. Hardy, Associate Professor of Otolaryngology and Director of the Hearing and Speech Clinic at the Johns Hopkins University School of Medicine, and Dr. Miriam Pauls, Assistant Professor of Otolaryngology at the Johns Hopkins School of Medi-

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cine, will discuss the problems of hearing. Dr. Harlan Bloomer, Professor of Speech and Director of Speech Clinic, University of Michigan, will talk on speech problems. Dr. A. D. Ruedemann, Medical Director of the Kresge Eye Institute and Chairman of the Department of Ophthalmology at Duane University Medical School, and Miss Patricia Spaulding, Research Psychologist of the Kresge Eye Institute, will discuss the problems of reading.

After the presentation of the papers and general summary the meeting will be open for questions.

HEARING DISORDERS

WILLIAM G. HARDY, PH.D., and MIRIAM D. PAULS, PH.D.

There are 3 elements in the preschool age child's development of normal communicative habits, hearing, language and speech. The presentation of sound to the mind is a fundamental step; the hearing mechanism is the antenna of the mind. A child learns to talk because he hears and he talks as he hears. Very few children are totally deaf, however; deafness is more a verbal than an organic entity, and there are many gradients between normal hearing and total hearing loss. When hearing is so profoundly impaired that the child gets nothing from ordinary speech-sounds, he learns to be a watcher, an imitator; this is apt to be a frustrating experience and he may become an aggressive 4 year old with a good many temper-tantrums.

Aside from well-known genetic or biologic sources, most nerve-type hearing impairments may be causally related not only to meningetic, encephalitic and tubercular invasions, but also to assault by many different types of virus-diseases and the common children's diseases, particularly in the first 6 or 8 months of life. In many of these problems, the perceptive mechanism of hearing is so damaged that the child hears something of everything but not enough of anything to be able to reproduce normal speech patterns.

A child with seriously impaired hearing may behave in different stages of development in many ways like children in many other categories related to retarded development. Differential diagnosis is often confused and confusing, but hearing impairment can be quite accurately specified now, and this measurement logically becomes an early step. In the nature of things, it devolves upon the pediatrician to take the first step, recognition of trouble that may be referable to hearing. Then he may make the necessary otologic referral. Many problems are medically irreversible. The child's needs may be quite diverse. Once diagnostic and evaluative procedures are completed, and all indicated medical and surgical treatment applied, then, and only then can reasonable steps be taken to promote the best possible development of each child's communicative needs.

In a recent study of 572 children, ranging in age from 4 months to 5 years, all of whom were communicatively aberrant, 116 had normal hearing, while 456 had impaired hearing. Of the 456, 17% had a mild impairment, 24% a moderate loss, 32%, a severe loss, and 27% a profound impairment. The mean hearing impairment, from all causes, is 61 db. None had a total impairment.

Children with impairment down to 75 db. below normal can make use of audition as the major pathway for language comprehension, with visual stimuli as adjuncts. They are within reach of a wearable hearing aid. It has been repeatedly demonstrated that with constant amplification, most of these children can learn to hear. It takes about 2 years of constant exposure to normal language and speech to develop useful auditory patterns in the small mind. With very young children this development is best centered around the home and the activities of daily living. By the time they are 4 or 5, they will be ready for intensive training in language skills. The goal is a regular school with whatever appropriate special help in communicative skills and learning is needed. For some who are slow in learning, or with a poor home environment, this may not be achievable.

The other children, with impairment greater than 75 db., must learn to communicate principally by use of vision, with audition as a limited adjunct. They will usually require long-term intensive special education in a school for the deaf.

There are several basic concepts applicable to these problems: (1) hearing rehabilitation is many-sided, and requires professional and parental teamwork; (2) communication is an entity, involving hearing, language and speech; (3) treatment and training must be based on careful diagnosis and functional measurement; (4) treatment and training should be started as early as possible, the ages 2 to 5 being most important; (5) most children can learn to talk; (6) most children can utilize amplified sound provided it is started at an early age and made an integral part of the developing mind; (7) most children make the best adjustment to an aid between 2 and 3 years of age; the most

serious error comes in waiting too long; (8) the question is not whether special training is necessary, but how much and what kind of special training; (9) most children develop best in a situation that is the closest approach to normalcy, provided their special needs are met; (10) parent-understanding and parent-guidance are the keys to early steps in training the child with hearing impairment. Each child is a unique individual with his own particular needs to be met.

SPEECH DISORDERS

HARLAN BLOOMER, M.D.

Approximately 5 to 10% of children do not develop normal speech by the time they are 7 or 8 years of age, and 3 to 4% will not make a satisfactory adjustment after that time unless they receive special help. Defective speech frequently affects the growing child adversely because it contributes to a low evaluation of personal worth, and it eventually handicaps him by reducing his social acceptability, limits his educational goals, and reduces his employment opportunities.

Eight major classifications of speech disorder are distinguished:

1. Articulatory disorders—omissions, distortions, substitutions, or additions of vowels or consonants;
2. Stuttering—repetition, blocking, prolongations, or use of avoidance devices in speech;
3. Voice disorders—affecting quality, loudness, pitch or melody of voice;
4. Delayed speech—descriptive of retardation in verbal usage;
5. Aphasia—loss of expression or reception of speech, due to trauma to cortical association areas;
6. Cleft palate—affecting articulation and voice characteristics;
7. Cerebral palsy—affecting articulation, voice, rhythm and sometimes language acquisition; and
8. Hearing loss—affecting articulation, voice, rhythm and language acquisition.

The existence of one or more of these speech symptoms is to be interpreted as an indication of an abnormal pattern of development; the symptoms are useful warning signs that a careful appraisal of the physical, emotional and environmental status of the child should be undertaken.

The majority of speech defects have their origin in the events of early childhood. The etiology of such disorders is to be sought in multiple events, cumulative in effect, rather than in single causes or events. This viewpoint emphasizes the usefulness of aberrations in voice as diagnostic signs of physical and emotional disturbance. Stuttering is a symptom which often indicates underlying tensions in the child which should not be ignored although often there is much to be gained by not calling the child's attention to the stuttering behavior. Articulatory defects arise from many causes, of which infected tonsils and adenoids, and tongue tie have been given attention far out of proportion to their significance. The effects of even such abnormalities as cleft lip and palate, and cerebral palsy, as well as the so-called "functional" problems can often be minimized greatly by early parental support and proper medical care and environmental management.

Professional help in diagnosis and therapy for speech problems is generally available through the larger university and college clinics. The American Speech and Hearing Association maintains a directory of qualified speech clinicians available through the *Journal of Speech and Hearing Disorders,* edited by Grant Fairbanks, University of Illinois at Urbana.

In summary, it is pointed out (1) that there is need for both prevention and treatment programs, (2) that professional interdisciplinary cooperation is required in the successful study and treatment of children with speech disorders, (3) that speech defects should be interpreted within a framework of child growth and development, stressing early environmental, physical and emotional influences in the emergence of abnormal speech patterns and (4) that there are facilities available to assist the pediatrician in providing adequate speech diagnosis and therapy for the children under his care.

READING DIFFICULTIES

A. D. RUEDEMANN, M.D.

During the past 30 years, I have been extremely interested in foveal coordination and more specifically in the effort that it has on the individual who does not enjoy complete coordination. So much has been written about the extraocular muscles that it seems rather trite to attempt to present a different thought on this complex, compound subject. It is really an anatomic, physiologic, psychologic complex and there are so many factors involved that one loses himself in theory long before

the practical results have started through. The entire problem is shrouded in the mystery of the fovea, its sensitivity levels, its relative and important recording center in the brain, and finally the development of the fusion center. This discussion will refer only to two-eyed people. The one-eyed individual with a good fovea learns by experience the sense of depth, width and height and carries on a perfectly normal existence within his visual limitation. The two-eyed individual is an entirely different animal, the second eye being extremely important whether it has a complete fovea or not. The absence of the fovea or its complete loss is of much more value to the individual than a fovea that is partly lost or not definitely interfered with. In our special study of foveal coordination which we began some 4 years ago, it became immediately apparent that we could not use the older group of individuals because of secondary psychologic changes that interfere with our study.

There are actually 3 sets of muscles involved in vision that relate to the fovea. The first is the ciliary iris combination, the iris cutting down the stray radiation, and the ciliary body fixing the image on the fovea. Second are the extraocular muscles which place the fovea in position and once both foveas are set to observe, especially for panoramic observation, the neck muscles carry out and allow an arc of better than 180° binocular foveal coordination. The entire function of the extraocular muscles is to fixate the fovea. They are unable to move the eye for any other reason. They cannot maintain fixation of any part of the eye except the fovea and they are under the complete direction of the fovea at all times. The entire musculature that is associated with the eye problem is anatomically much more than sufficient and physiologically is capable beyond the greatest normal requirements of normal foveas. The neck muscles, of which there are 22, are also more than sufficient for their needs. It requires tremendous excess use of the ciliary muscles, extraocular muscles, and neck muscles to produce discomfort due to normal muscle fatigue. Early observation of the foveas in the newborn infant shows a diffuse area, even more indifferent than we see in the adult, but it is a fovea that is equal to the brain capacity of the individual.

It would be well to mention at this time the psychologic study that we have been making on these young individuals in the hope of ascertaining what mental level we are dealing with. In the first place, the psychologic tests that have been heretofore used are of little or no value, and our first group of so-called child psychologists gave us so much faulty information that we could not use it in our statistical study. It was a hit and miss campaign, mostly on the miss side, for a very good reason. Child psychologists have centered most of their interest in study on visual tests. The group that we were interested in already were having difficulty with their vision. I believe that I can honestly say that the initial studies done psychologically did not help us in arriving at a good conclusion.

Our second year's studies were definitely better because the psychologists were forced to evolve tests that would reveal certain visual memory patterns. Now we are beginning to find out what the approximate intelligence level of these young children is when they head for school. The reason for this psychologic study is that over a period of years, keeping very accurate studies of the end results of ocular muscle surgery, I have been embarrassed and chagrined many times by the tendency of the muscles to revert to their previous position. The central vision in the operated eye is not maintained and although the youngster is somewhat improved, many are unable to carry on in an intelligent level equal to their age and normal social group. There has been and is something drastically missing in our handling of the normal so-called muscle problem. Over a period of years, the records of these cases have been reported visually in a photographic way without records as to their fusional end results, taken at periods long enough after the surgery has been instituted to warrant listing them as cures. From this study of my own statistics, for the sake of the records, I might say that we have cosmetically straightened 80% of our cases, at least giving a good anatomic correction. This is truly a cosmetic result and has little to do with the physiopsychologic-intellectual level of the individual upon which the operation has been performed. By chance, with some orthoptics we have held about 10% of this group in second grade fusion and less than 10% in third degree fusion. It was my contention as long as 20 years ago that unless we carried these patients completely to third degree fusion and they could hold this fusion over long enough periods of time, we were developing our own group of neurotics, our own group of people who had nervous breakdowns, and people with inferior intellectual abilities.

When I came to Detroit I was able to interest the Kresge Foundation in making a basic study on the visual levels of children in the school ages, and we started with those in high school, intermediate school and the grade school. It became apparent to us, almost immediately, that by the time these youngsters entered the first grade, their visual pattern had been very well set down and

we were going to have a great deal of difficulty in making any change in it. During the past 2 years we have limited our study to those in the grade schools that we had studied previously; those who were having difficulty in school and were behavior problems. With a team of child psychologists and orthoptic technicians and an oculist, we have made as complete an ocular study on individuals as is possible under our present day knowledge. We are seeing babies as young as 4 weeks and up through the pre-school group and the low grades to the sixth grade level.

It is apparent to me now that each eye develops its own foveal-muscular brain pattern and as the vision in the fovea develops, the central foveal area progresses parallel with it. As the 2 eyes reach a fairly level state, the 2 foveas must be coordinated with a central fusion center. The individual eye pattern is a firmly developed one and each eye establishes its own eye brain pattern with a firmness that is difficult to interfere with. These patterns are just as definite in the negative phase as they are in the positive phase. By that I mean when the pattern is not one of fusion or of coordination, children are just as definite in maintaining the faulty coordination as they are the normal one. With this state existing, it becomes immediately apparent that the eye-brain pattern, once firmly established, is difficult to correct or to change and the importance of the normal physiologic state becomes more and more important. The ciliary muscle, the shape of the iris, the foveal sensitivity are all paramount in the establishment of normal fusion patterns. The stimulation through the fovea then directs extraocular mucles and, except for the occasional case of myositis or other anatomic muscle changes, the entire pattern is one directed by normal foveal fixation.

Early study of the fovea is extremely important to ascertain whether one is dealing with a normal anatomic fovea or one that has been interfered with or where there is a congenital defect or something that will retard the normal visual increase as the youngster develops. Foveal coordination starts at an early age. We have been able to spot it in youngsters at the age of 28 days, at which time a youngster will fix on simple objects with both eyes simultaneously and hold fixation. If at this time the youngsters should learn not to hold fixation, they will be just as definite in not holding fixation as they are in holding it, and the deviations become as apparent and as direct as does the tendency to hold the normal eye brain pattern. The correcting mechanisms must start at this time. If the individual is allowed to firmly establish the incorrect eye brain pattern, the problem becomes increasingly difficult as time elapses. After a period of a few years, it becomes completely impossible to obtain a good fusional result. Interruption of the incorrect foveal muscle brain pattern must take place as near the time of onset as is possible. The longer one waits the less the opportunity. With a realistic approach to foveal coordination it makes it possible to give a logical sequence of events to the many psychologic deviations that we find in these individuals. First, it is apparent that a baby learns by visual imitation. He watches and attempts to perform with his normal coordination. When both foveas act simultaneously the coordination reflex becomes complete. Without completion, there must be a certain amount of hesitancy, inaccuracy and a definite amount of mental disturbance. It is my belief that many of our psychologic "offshoots," inferiority complexes, and the like are secondary to the lack of foveal coordination the individual has. As the deviation persists, it regulates the individual's inability to coordinate the hand, walking, and indirectly his speech. It also seems quite likely that because of the visual uncertainty, should the youngster be fortunate enough to have a normal pair of ears, he may substitute hearing as his basic pattern for learning, and this substitute may become so firmly fixed that it forms a barrier to our re-education of the visual pattern. The individual has become primarily an auditory learner. Lack of concentration, a short span of attention, inability to learn to read visually are all part of this lack of foveal coordination, and the future pattern for the individual is set long before he enters the first grade of school. Our findings indicate that 20% of the preschool group have some lack of foveal coordination. Some of these, through ocular development, lose their accommodative difficulties to a great extent, and some of them take on convergence insufficiencies which definitely increase during the first year in school. Among the preschool group many muscle errors that were only relative now become fixed and permanent. Those errors that are associated with the muscle of accommodation are the best handled and can be completely corrected in most instances without surgery. Those in which there has been a diminution in vision usually can be corrected without surgery and one fovea can be restored to normal level. If surgery is necessary, it does not have to be too profound. Interference of the spastic muscle will suffice. Once this has been accomplished, however, re-education must take place immediately and must be done thoroughly. The amount of surgery or recession or resection or tuck is only of importance in the interference of the eyebrain pattern. If the foveas have been equalized in vision or nearly

so, one interrupts the major deviation, and then by as much visual impact as possible re-educates the youngster in the normal visual pattern as completely and thoroughly and as early as possible after the surgery. If the youngster does not cooperate or the cooperation is poor from the family side, it is only a short period of time before it is impossible to re-educate the youngster and the tendency to deviate back to its previous position commences almost at once. The earlier we are able to interrupt the faulty muscle-brain pattern, the less difficulty in developing fusion. Incidence of corrections that do not form a vertical component, and as our knowledge of the fovea with its irregularities and deficiencies increases our improvements will be more constant. As is generally known, all general infection apparently affects the sensitivity and foveal coordination, some much more than others. It does seem that certain diseases such as varicella and rubeola have a definite effect on foveal sensitivity. Whether it is the cerebral fovea or the ocular fovea, we are unable to ascertain. Suffice it to say at this time that there is a definite effect on foveal sensitivity following certain of the viral diseases. In the light of our present knowledge and statistical end result, it becomes apparent that one should find out as early as possible. When a foveal level is ascertained one can then differentiate those that have a possibility of getting good fusion or some fusion and dividing them from those on which it is primarily essential to operate only for cosmetic results. And finally, the third group are those who have severe deviations in any direction and these must be corrected therapeutically. Because of the wide angles of deviation they have a definite deleterious effect on the nervous system of any individual. The vertical errors are extremely important and must be corrected within one degree. Those that do not reach this level of correction must be corrected by vertical prisms. The development of the fusion center is almost impossible without good vertical coordination. The eyes can not tolerate vertical diplopia in any shape, form or manner.

The psychologic study of these individuals has raised our interest in finding out what happens to these people as they go into higher levels of study. Apparently, they all do fairly well up until the second and third year of high school when they take a nose dive, become disinterested; many of them quit, and others fail to reach college level. Those who are fortunate enough by stint of association or determination can make college level but do not level off into the first third of their class. They have much difficulty scholastically and socially. A large number of them have nervous breakdowns during the semester examination; others become deviates in behavior. It is our contention that complete foveal coordination that is constantly maintained is the most important learning sense of the individual.

If we might summarize what we have learned to date, complete constant foveal coordination is the most important learning sense. Second, any vertical coordination must be corrected within one or less degree. The foveal vision levels must be nearly equal or in the highest level of vision for both eyes or true coordination cannot be obtained. The earlier the incoordination is diagnosed and the more complete the foveal education, the more complete will be fusional end results. The key to the success of re-education is the building of the individual's use of the fovea, early diagnosis and re-education to precede the muscle surgery, which in itself is only a means of interrupting the faulty eye-brain pattern.

SUMMARY

JOHN E. BORDLEY, M.D.

It has been evident this afternoon what a close interrelationship there is between the 3 subjects on our program; as an example, we heard Dr. Hardy state that hearing was the most important sense for intellectual development. Miss Spaulding also made the same statement concerning vision, whereas I believe it is safe to say that Dr. Bloomer feels that speech is absolutely essential for a child's normal development. Dr. Hardy in his paper stressed the wisdom of apprehending hearing loss early. Such investigation should always be made when communicative disorders are suspect. He explained the special technics at hand to make early diagnosis possible. Early diagnosis, he explained, makes early rehabilitation much easier to plan and it allows for individual planning for the patient according to his actual hearing loss.

Dr. Pauls showed that with modern technics the hearing handicapped child has a much brighter future than 15 years ago. She explained the significance of the value of the various hearing levels obtainable by modern diagnostic technics. She spoke convincingly for early amplification, where it can be used for the hard-of-hearing child, and she stated that emphasis should be on "hearing"

and not on "deafness." Her plea, throughout her paper, reiterates again and again that the best course of rehabilitation should always stress the maintenance of a normal environment whenever possible.

Both Dr. Pauls and Dr. Bloomer emphasized that speech development is best fostered by a maternal bath of sound. Dr. Bloomer, in his presentation, stated that the preventability of speech problems is more important than curing speech difficulties. Seventy-five per cent of such problems could be handled successfully by coordinating medical care, emotional growth and satisfactory parent-child relationship. Twenty-five per cent of speech problems, although resulting from actual physical damage, would be helped if the climactic effect of such damage could be minimized by proper handling of the children.

Dr. Ruedemann spoke on the relations of strabismus in learning. He felt that there should be as much emphasis on its correction for the functional value of the vision as well as for any cosmetic effect. Foveal vision, he stated, has a special application to learning. Lack of such coordination in the eyes affects concentration and also affects visual memory. He showed how the muscles put the fovea in the correct relation for eye correlation. He also stressed early diagnosis and early corrective work, and he spoke of the importance of visual capacity instead of vision *per se*.

Miss Spaulding presented an excellent summary of her research in which she showed the rate of instance of muscle imbalance in children, and how that imbalance seems to increase from lower to higher age groups. A greater proportion of abnormals seems to always be found in the older groups of children. This is especially true of strabismus. She feels that the superiority of some of the abnormals over the controls make it evident that muscle error is not necessarily associated with less than average learning ability. Like Dr. Pauls and Dr. Bloomer, she feels that a positive approach should be emphasized, and that the child should be shown what he can do rather than what he can't.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussions could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

DEAR DR. HARPER:

The General Assembly, the Social Commission and the Economic and Social Council of the World Health Organization are to discuss the future of the United Nations' International Children's Emergency Fund during this year of 1953.

Editorials have appeared in the press (*New York Times,* Apr. 6, 1953 and Chicago *Daily Sun-Times,* May 27, 1953) criticizing our government for not having paid U.N.I.C.E.F. its 1953 voluntary contribution of $9,814,000.

A number of Fellows of the American Academy of Pediatrics have become concerned as to the plight in which U.N.I.C.E.F. finds itself and requested the matter be brought to the attention of the Executive Board at its meeting May 28-31, 1953 in Evanston. It was the opinion of the members contacting the Board that the work of the U.N.I.C.E.F. should be continued.

The presence of this item on the agenda inspired the preparation of the enclosed resume of the evolution of W.H.O. and U.N.I.C.E.F. As the Executive Board found this information of value, they have suggested that it might be made available to other Fellows through publication in your section in PEDIATRICS.

Our members may also be interested in the resolution passed by the Executive Board after deliberating on this subject.

STEWART H. CLIFFORD, M.D.
Chairman, District I

THE EVOLUTION OF W.H.O. AND U.N.I.C.E.F.
1943-1946

United Nations' Relief and Rehabilitation Administration

Established in 1943 as the first service agency of the United Nations. Its assistance included relief supplies, food, clothing, health and welfare services. Even by 1946 the extensive aid given by U.N.R.R.A. was insufficient to meet the needs. The mortality rate for children was still high and there was a shortage of food, fuel, clothing and other necessities. Many schools and institutions for children were destroyed and rebuilding was retarded for lack of materials.

In August 1946 U.N.R.R.A. seeking to terminate its emergency activities adopted the following resolutions:

1. Transfer the U.N.R.R.A.'s major health activities to the W.H.O. or its interim commission
2. Transfer to the U.N. whatever social welfare functions that body desired to undertake
3. Transfer displaced persons operations to I.R.O.
4. Create the International Children's Emergency Fund for the rehabilitation of children and adolescents of liberated countries.

1946	
U.N.I.C.E.F.	W.H.O.
The International Children's Emergency Fund was established in Dec. 1946 with headquarters at Lake Success, N.Y. for the rehabilitation of children and adolescents of liberated countries.	Under the United Nations' Charter the responsibility in the field of economic and social cooperation was vested in the general assembly and in the Economic and Social Council, acting under authority of the general assembly. The E.S.C. adopted a resolution in Feb. 1946 to establish an international health organization. At a conference in New York, June 19-July 22, 1946, 61 states signed a proposed constitution of a World Health Organization.
1947	
U.N.I.C.E.F. provided a daily supplementary meal to 3,000,000 European children. U.N.I.C.E.F. proposed to use its resources for: 1. Supplementing essential food and other supplies needed to alleviate malnutrition and disease in children and to guard the health of expectant and nursing mothers. 2. Encourage the re-establishment of children's institutions and services destroyed by war through supplying clothes, shoes, cod liver oil and medical supplies. 3. Enlisting the cooperation of the U.N. and other organizations in giving assistance for	W.H.O.'s constitution was shy two states of ratification. It functioned through an interim commission. It took over the functions of the League of Nation's Health Organization. It assisted in combating an epidemic of cholera in Egypt. It developed a long range program for malaria and tuberculosis. It provided technical aid and put into operation a program to send doctors and health experts to study in world centers of medical knowledge.

U.N.I.C.E.F.	W.H.O.
fellowships for the training of health and welfare personnel for children's work. By Dec. 1947, $38,932,000 had been contributed or pledged to U.N.I.C.E.F. Fourteen governments contributed $27,267,000 and the balance of $11,665,000 from other sources, mostly U.N.R.R.A. assets.	

The U.N. general assembly in its second session approved agreements defining the relationship of the U.N. to I.C.E.F. and to W.H.O. among others. These agreements, because of the specialized character of certain agencies, contained features not found in earlier agreements. In particular the agreement with I.C.E.F. went less far than other agreements in providing the U.N. with effective means of coordinating the activities of the specialized agencies with those of the U.N.

1948

Continued supplemental feeding.	The W.H.O. with headquarters in Geneva became a specialized agency of U.N. on April 7, 1948 when 26 countries had ratified its constitution.

In a joint effort with W.H.O., I.C.E.F. took steps to combat health hazards—especially tuberculosis and syphilis.

Contributions or pledges to I.C.E.F. from governments in 1948 totaled $62,000,000. Voluntary contributions through the United Nations' Appeal for Children added $10,000,000.	The World Health Assembly adopted a program giving top priority to: malaria, tuberculosis, venereal disease; maternal and child health, sanitary engineering and environmental hygiene and public health administration. A budget for 1948 of $4,800,000 was approved.

1949

The work of the U.N.I.C.E.F. was not restricted to national boundaries—it had programs on both sides in war-torn China and on both sides of the "Iron Curtain." It supplied medicine, equipment and training for local personnel for treating tuberculosis, malaria, syphilis, yaws in Asia.	W.H.O. gave priority to children in much of its work. It surveyed the tuberculosis problem in many countries and set up laboratories to manufacture B.C.G. vaccine. W.H.O. conducted a sanitation program and in some areas infant mortality fell from 300 to 30 per 1,000 in a comparatively short time.

In a joint operation with W.H.O., a tuberculosis testing program was conducted in Europe and North Africa.

W.H.O. and U.N.I.C.E.F. jointly conducted a program on malarial control with great success in 13 countries reducing incidence, reclaiming malarial infested agricultural dis-

tricts—in some areas food production was increased 70%.

W.H.O. and U.N.I.C.E.F. jointly attacked venereal disease that affected nearly half the population in some regions.

U.N.I.C.E.F.	W.H.O.
In the two years 1948-1949 U.N.I.C.E.F. received a total of $141,000,000. ⅔ of this from 36 governments ($70,000,000 from the U.S.A.) $32,000,000 from assets of U.N.R.R.A. and $10,000,000 from popular appeal.	W.H.O. in 1949 had a budget of $7,873,000 and a supplementary budget of $9,152,250 to be raised on a voluntary basis. (In 1949 the Pan American Sanitary Bureau P.A.S.B. became the W.H.O. regional office for the Americas.)
1950	
U.N.I.C.E.F. had completed the first phase of its operations by Dec. 1, 1950. It had provided $150,000,000 mostly in food, clothing, health supplies and services to children in war-devastated countries. In much of the work U.N.I.C.E.F. provided supplies and equipment. On Dec. 1, 1950 U.N.I.C.E.F. was continued for another three years by action of the general assembly of the U.N. with the presumption that in 1953 it would be made permanent. The second phase of U.N.I.C.E.F. begun Dec. 1, 1950 would emphasize the continuing needs of children in countries of limited economic development, strengthening wherever possible the permanent child health and welfare programs and still taking into account the needs which were decreasing in most war-devastated countries. Allocations late in 1950 for the work of U.N.I.C.E.F.: $2,532,000 to 9 Asiatic countries 500,000 to Korea for maternal and child health projects 840,000 to Latin America 528,000 to 9 Latin American countries 500,000 for health services and relief in the Middle East 350,000 for B.C.G. in Iraq 150,000 for anti bejel-syphilis in Iraq 185,000 for food for 1,000,000 Greek children 586,000 for food for 1,400,000 Yugoslav children	W.H.O.'s program was to expand and intensify its activities acting both independently and in cooperation. Its program included malaria, tuberculosis and the production of penicillin. W.H.O. again gave priority to children. In much of the work W.H.O. provided technical advice and assistance. W.H.O. reorganized into three divisions—public health services, communicable diseases and professional and technical education. The maternal and child health section of W.H.O. developed a long-range program: 1. Stimulation of research and investigation of conditions affecting the well-being of children. 2. Provision of technical information. 3. Provision of expert advisers and demonstration teams to underdeveloped countries and to other countries requesting them. 4. Expansion of existing fellowships and training programs, including the training of nurses, nurses' aides, midwives, nutritionists, health educators and physicians. 5. Instruction in mental health for all persons thus trained in maternal and child health. 6. Cooperation with U.N.I.C.E.F. in organization of maternity services and all kinds of child health clinics, including clinics for handicapped children and child guidance clinics and the extension of mass immunization campaigns. W.H.O.'s budget for 1950 was $6,300,000.

1951

U.N.I.C.E.F.	W.H.O.
This was the first year of U.N.I.C.E.F.'s "second phase." Example of U.N.I.C.E.F.'s program: Provided supplies and equipment for a two-year maternal and child health program in Burma. The objective was: 1. Establish a pediatric department in the Rangoon General Hospital. 2. Increase the diagnosis and treatment of syphilis and to improve the supply of penicillin. 3. Reorganize the children's wards and improve the equipment in two hospitals and at the Mothers' and Children's Welfare Clinics. 4. Improve the facilities for teaching maternal and child health to doctors, nurses, midwives and other public health workers. 5. Expansion of school health services. 6. A general strengthening of the Burmese health services by the provision of fellowships for study abroad.	May 7-25, 1951 W.H. assembly developed a world-wide coordinated program. Regardless of the sources of funds available the integration of services for 1952 was to include the activities of three of the specialized agencies of the U.N.: U.N.I.C.E.F.; the Program of Technical Assistance for Economic Development, and the W.H.O. In Feb. 1951 started a field project for training nurses, health visitors and midwives in a rural area near New Delhi, India. The Scandinavian Red Cross withdrew from the anti-tuberculosis campaign and this work was carried on by W.H.O. with the assistance of U.N.I.C.E.F. W.H.O. provided 12 international experts for U.N.I.C.E.F.'s Burma program—the government of Burma provides a like number of their counterparts.

W.H.O. and U.N.I.C.E.F. added impressive gains in their campaigns against malaria, syphilis, tuberculosis, typhoid, typhus, yaws and other communicable diseases. Environmental sanitation was promoted in many areas of the world.

U.N.I.C.E.F.'s budget was "a small fraction of the amount spent annually during the first years of the fund's existence."	W.H.O.'s budget for 1951 was $6,300,000.

1952

In 1952 one of the continuing problems with which the principal organs of the U.N. dealt was that of better coordination of the policies and activities of the United Nations and the specialized agencies in order to prevent overlapping and achieve concentration on tasks of primary importance.

At its sixth session in Feb. 1952 the U.N. general assembly approved the system of priorities which had been adopted by the Economic and Social council as a coordinating device.

1. Increased food production and distribution
2. Increased production in fields other than food
3. Measures for promoting domestic full employment and economic stability within an expanding economy
4. Acceleration of welfare, social security and basic public health program

5. Development of education and science.
6. Formulation and wider observance of human rights

In 1952 U.N.I.C.E.F. sustained extensive programs under its own auspices or in cooperation with the Food and Agricultural organization (F.A.O.) or with W.H.O. in all cases working with the government agencies in the countries assisted.

The major types of U.N.I.C.E.F. assistance were:

1. General maternal and child health services.
2. B.C.G. vaccination and other tuberculosis control measures.
3. Campaigns against bejel, syphilis and yaws.
4. Anti-malarial and insect control measures.
5. Immunization against diphtheria and whooping cough.
6. Aid in the production of antibiotics and insecticides.
7. Child feeding.
8. Milk conservation.
9. Clothing, shoes, shelter and miscellaneous supplies.

Dried skim milk was provided in large quantities in several underdeveloped countries where severe nutritional deficiencies prevailed among children.

Most of the resources of U.N.I.C.E.F. in 1952 were used in the development of elementary health and welfare services.

In contrast with its tremendous emergency feeding program during the first years, the 1952 emphasis was on long range projects whereby countries could lay a basis for more adequate feeding of their own children and for reduced illness and death among children.

In 1952 W.H.O. changed its approach—the public health administration of member states must take the initiative on their own programs—W.H.O. to give advice and guidance if requested—the local region to submit its program and budget to W.H.O.

W.H.O. now had 79 full member states and 3 associate members.

The W.H.O. defined six major health problems on which the efforts of the organization were to be concentrated:

1. W.H.O. assisted malarial control in 20 countries.
2. Tuberculosis control—demonstration and training centers in 13 countries and mass vaccination with B.C.G. in 18 countries (the latter with U.N.I.C.E.F.)
3. Venereal disease and
4. Treponematoses, W.H.O. assisted in penicillin treatment in 9 countries. In nonvenereal treponematoses (yaws, bejel, pinta) 6,000,000 people examined and 2,000,000 penicillin treated.
5. Maternal and child health projects launched with W.H.O.'s assistance and in many cases with supplies from U.N.I.C.E.F. in 15 countries. Ten European countries, Lebanon and Japan received W.H.O. assistance in the rehabilitation of physically handicapped children or in the care of premature infants.
6. Environmental sanitary problems.

The first four years of W.H.O. saw unprecedented reduction in death rates in many countries and even greater reduction in morbidity. Control of most deadly communicable disease was greatly advanced; increased production of food was assured as was the protection of food and water through public health measures. In all continents where malaria, plague, syphilis, trachoma, tuberculosis, typhoid fever, typhus and yellow fever traditionally had been prevalent, progress was made. During the year ending in the summer of 1952, 7,255,122 tests for tuberculosis were given and of those tested 3,512,716 were vaccinated.

W.H.O. evidenced a growing interest in mental hygiene in 1952:

1. A seminary on mental health and infant development held in Chichester, England,

U.N.I.C.E.F.	W.H.O.
	attended by doctors, nurses and social workers from 28 countries and territories. 2. A conference of experts on mental health aspects of adoption in New York. Questions considered: what are the factors relating to the emotional and psychological development of the child that should be taken into consideration in the adoption process? What are the factors that relate to the emotional needs of the adoptive parents that should be taken into consideration? What factors should be considered that relate to the emotional needs of the natural mother who decides to relinquish her child?
U.N.I.C.E.F.'s budget for 1952—$14,013,000.	W.H.O.'s budget for 1952—$7,700,000.
1953	
Budget requested for 1953—$15,000,000. "I believe it would be a tragic mistake and an appalling setback of America's entire humanitarian record if Congress did not remedy the omission of funds for U.N.I.C.E.F. For a comparative pittance we and like minded nations have achieved magnificent results for their youngsters and their mothers. All that remains is to find a prompt form of legislation to include an adequate stop-gap appropriation for U.N.I.C.E.F." Senator Alexander Wiley U.N.I.C.E.F. has allotted $5,300,000 to going programs in 30 countries. It has $2,600 in its treasury. The U.S.A. has not made good on its pledge of $9,814,000.	Budget requested for 1953—$8,485,095.

SOURCES OF INFORMATION

Lenroot, Katharine F., Chief, Children's Bureau.
Child Welfare; Britannica Book of the Year 1947.
Goodrich, Leland M., Prof. of Political Science, Brown University, United Nations; Britannica Book of the Year 1947, 1948, 1949, 1950, 1951, 1952.
Nopkirk, Howard Williams, Executive Director, Child Welfare League of America; Child Welfare; Britannica Book of the Year 1948, 1949, 1950, 1951, 1952.
New York Times Editorial—The Children's Fund, April 6, 1953.

RESOLUTION PASSED BY THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

WHEREAS, the United Nations' International Children's Emergency Fund (U.N.I.C.E.F.) was established in 1946 in response to the then existing emergency, for

the rehabilitation of children and adolescents of countries which were victims of aggression and for child health purposes, generally, giving high priority to the children of countries victims of aggression, and

WHEREAS, in the first phase of its existence, from 1946-1949, U.N.I.C.E.F. fulfilled this emergency function in a most praiseworthy manner; however, when 1950 was reached U.N.I.C.E.F., having completed its original function, changed its objectives and entered into a second phase, not contemplated in the original directive; this second phase to continue to December 1953 when the future of U.N.I.C.E.F. would again be considered by the General Assembly, and

WHEREAS, at the time of the emergency situation in 1946 the World Health Organization's constitution had not been ratified thus necessitating the creation of U.N.I.C.E.F., and

WHEREAS, the World Health Organization's constitution was ratified in 1948 and today has 79 full member states and 3 associate members, and

WHEREAS, a review of the activities of U.N.I.C.E.F. and the W.H.O. shows much overlapping of interests and apparent duplication of function, as well as many joint cooperative undertakings, and

WHEREAS, one of the problems of the United Nations is a better coordination of the policies and activities of the U.N. and the specialized agencies to prevent overlapping and to achieve concentration on tasks of primary importance,

THEREFORE, it is the opinion of this Board that since both U.N.I.C.E.F. and W.H.O.'s maternal and child health sections appear to be interested in and carrying out, in general, the same type of activity, the overall objective of the welfare of children would be more efficiently and economically achieved if these activities were combined in one organization. It is therefore suggested that the activities of U.N.I.C.E.F. as an independent body terminate in December 1953 and that all of its functions be transferred to and incorporated within the existing framework of the World Health Organization.

NEWS AND ANNOUNCEMENTS

The following diplomates were certified by the American Board of Pediatrics, Inc.:

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Allison, Joseph, Murphy Army Hosp., Waltham, Mass.
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Whitman, Mark Allan, 522 W. Hortter St., Philadelphia
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The next oral examinations will be held in Miami, Oct. 9, 10 and 11, 1953.

EDITORIAL

THE Editorial Board has received resignations from Dr. Allan M. Butler, Boston, and Dr. L. Emmett Holt, Jr., New York City, from membership on the Board. These resignations have been approved and have been accepted by the Executive Board of the Academy of Pediatrics at its meeting in Chicago, on May 28 to 31, 1953.

Dr. Butler has been a member of the Editorial Board since the inception of PEDIATRICS in 1946. He has played a considerable part in initiating the publication of PEDIATRICS, in establishing its editorial policies, in maintaining a high standard of publication and in particular in rendering invaluable services in selecting correct material for publication. He has been an unfailing worker. The Editorial Board has approved his resignation with regret and wishes to acknowledge a great indebtedness to him.

Dr. Holt joined the Editorial Board at a later period. His services have been considerable and his acknowledged ability in the general field of pediatrics has assisted materially in the function of the Editorial Board.

The Editorial Board has recommended to the Executive Board for membership on the Editorial Board Dr. Charles A. Janeway, Boston, to succeed Dr. Butler and Dr. Charles D. May, Iowa City, to succeed Dr. Holt. The Executive Board has approved these two nominations to fill the unexpired terms. It is with great pleasure, therefore, that PEDIATRICS announces the accession of these two names to the Editorial Board. Dr. Janeway is Professor of Pediatrics and Chairman of the Department of Harvard University and Chief of the Children's Hospital of Boston. Dr. May is Professor of Pediatrics, Iowa State Medical School and Head of the Department.

He succeeded Dr. Philip C. Jeans recently. These two persons will strengthen the Editorial Board and their services in the special fields of their interests will be of value in publication procedure.

PEDIATRICS also announces the establishment of a special section on education. This section has been contemplated since the start of publication. Dr. Grover F. Powers, New Haven, has been appointed contributing editor of PEDIATRICS to be in charge of this section. Dr. Powers returns to membership of the Editorial Board in this new capacity after several years' absence. He will be assisted by the Committee on Medical Education of the Academy of Pediatrics. This new section will serve to bring to the attention of the readers various types of material in this field. Pediatric education will be its chief interest but matters of medical education in general will be covered. It is contemplated that education in general as it is used in pediatrics, and, therefore, of children will be included. This section will have the same general character as other sections of PEDIATRICS. It, too, will be an open forum for discussion and reporting; the editor will welcome contributions.